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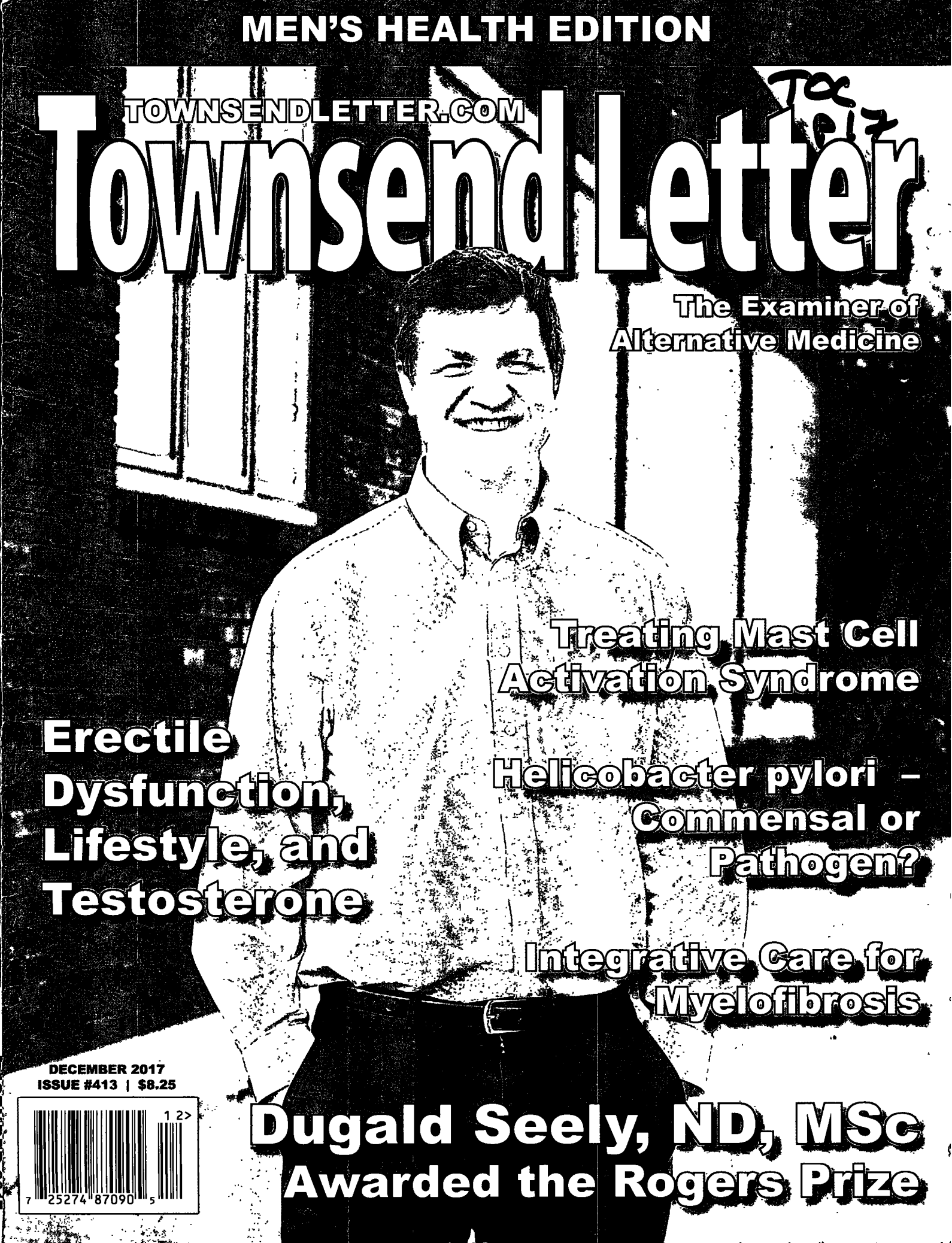

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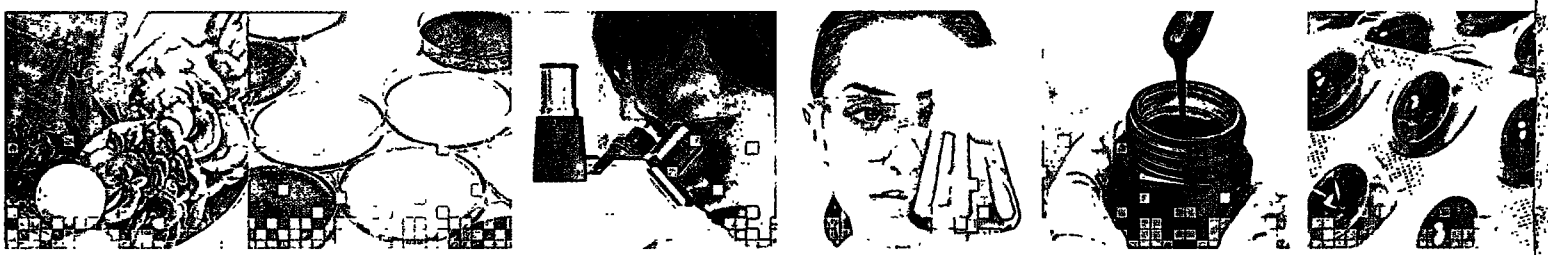

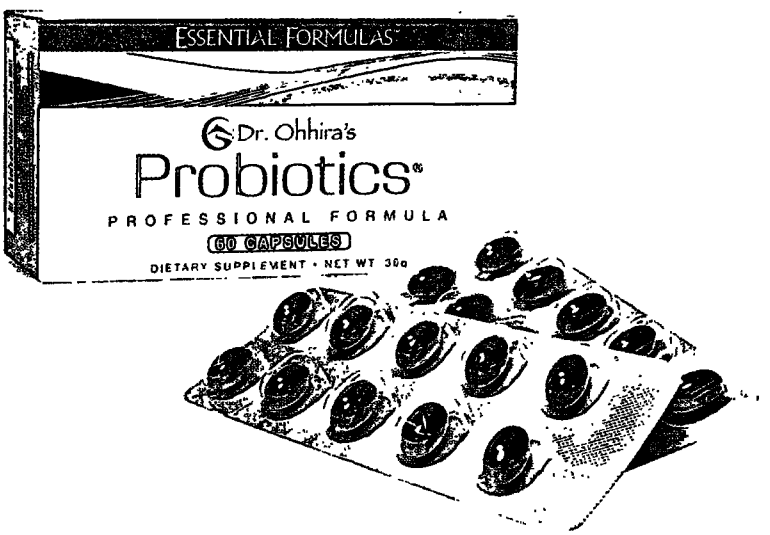

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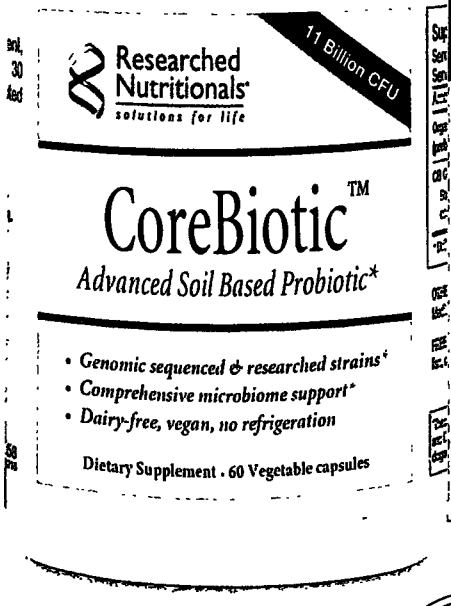

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Joseph Burrascano Jr., MD

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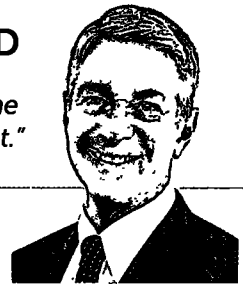

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From the Publisher

Chronic Wasting Disease (CWD)

Fall means one thing to most gun-owners – hunting season for elk and deer. Outdoorsmen relish the week they take off in the cold with fellow male hunters, spending hours trekking to find their animal often fruitlessly, but occasionally sighting a buck and, if lady luck avails, making the skilled shooting or bow kill. Dressing the downed animal in the field is obligatory especially of a heavy elk or moose. What that means is the hunter is exposed to the animal's blood, digestive tract and feces, bone and connective tissue, brain and musculature, with meat and blood particulates likely to be inhaled and ingested, and contamination of clothes and truck bed. Messy butchering is easily cleaned up with soap and water; not so easily addressed are tiny organisms known as prions that are infecting a growing number of cervids or reindeer, elk, and deer.

continued on page 10 ➤

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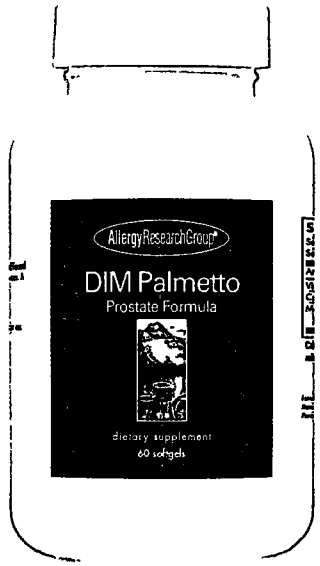

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Claire Farr: Portrait of a natural nutrition pioneer.

According to all who knew her, Claire Farr was a tireless crusader, genuine humanitarian, and dynamic entrepreneur with a "commitment to excellence for the nutritionally aware."

In 1969, driven by a personal struggle with severe food allergies and environmental sensitivities, Claire Farr set out on a mission to formulate and manufacture the highest quality, hypoallergenic nutritional supplements possible. As many dedicated entrepreneurs do, Claire set up shop in her own home in Carlsbad, California and Klaire Labs was born.

In her quest to develop a line of nutraceuticals that sensitive individuals could reliably tolerate, Claire initially focused on single ingredient formulations. Unlike most nutritional supplement manufacturers at the time, Claire purchased only pharmaceutical grade raw ingredients selected specifically for maximum purity and bioavailability. She avoided the use of fillers and synthetic ingredients, while focusing on natural and synergistic constituents. The medical community began to take notice.

By this time, demand was growing for environmental, nutrition-focused, and integrative medical practitioners. As such, Claire and her unique products gained the attention and respect of a number of prestigious complementary medicine proponents including: Theron Randolph, MD, Abram Hoffer, MD, PhD, Bernard Rimland, PhD, and William Crook, MD.

Word of consistently reliable outcomes spread, allowing Claire's home-based start-up to grow into a new manufacturing facility, expanding her capabilities to include bottling and custom formulations. It was not until 1983 that Claire introduced her first probiotic, a product category that ultimately became her most successful. Klaire Labs Ther-Biotic formulations remain a leading professional brand to this day.

In 2004, Klaire Labs was sold to ProThera, Inc. ProThera, Inc. was in turn acquired by Soho Flordis International (SFI) in 2013. SFI's philosophy to empower healthcare providers with better, natural options aligned quite naturally with that of Claire Farr. Having dedicated their lives' work to similar goals, the SFI founders represented a renewed commitment to, and a tangible investment in, Claire's founding principles.

In 2017, SFI USA (comprised of the three originating companies: ProThera, Inc., Klaire Labs, and Complementary Prescriptions) christened a new >75,000 square foot, state-of-the-art manufacturing facility, including expanded scientific and support resources, advanced quality tools, and modernized processes.

Although SFI has acquired several exceptionally discriminating, independent nutraceutical manufacturers across the globe in recent years, shared values are the common thread. In the spirit of honoring the past as we embrace the future, all products manufactured at SFI USA in Reno, Nevada will soon be unified under the Klaire Labs brand and guiding philosophy.

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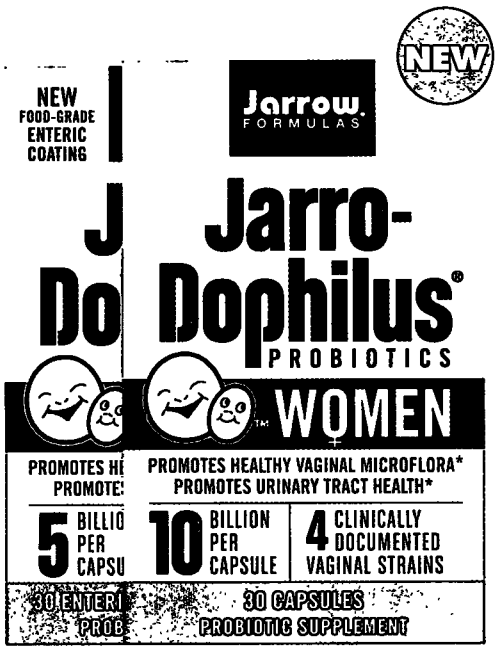

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Clinical Study #1 (1999)

In a study of 319 women visiting three medical clinics, most women's normal vaginal bacterial residents included *L. crispatus* (32%), followed by *L. jensenii* (23%), *L.* 1086V (15%), *L. gasseri* (5%), *L. fermentum* (0.3%), *L. oris* (0.3%), *L. reuteri* (0.3%), *L. ruminis* (0.3%), and *L. vaginalis* (0.3%).*

Antonio MAD, *et al. Journal of Infectious Diseases* 1999;180:1950–6.

Clinical Study #2 (2007)

In another study involving 126 healthy pregnant women, *L. crispatus* and *L. gasseri* were the most dominant species found, followed by *L. jensenii* and *L. rhamnosus.**

Kiss H, *et al. BJOG: An International Journal of Obstetrics & Gynaecology* 2007;114: 1402-1407.

Clinical Study #3 (2014)

In a double-blind, randomized placebo-controlled trial, 1-week of oral supplementation with the four Astarte strains significantly enriched *Lactobacilli* in the vaginal tract and reduced Nugent score in the neo-vagina of post-operative transsexual women, an environment typically resistant to colonization by *Lactobacilli.*

Kaufmann U, *et al. Eur J Obstet Gynecol Reprod Biol.* 2014 Jan;172:102-5.

Clinical Study #4 (2016)

In immunosuppressed pregnant women with herpes infection, oral supplementation with the four Astarte strains significantly reduced undesirable microbes in the intestines and vagina, and simultaneously increased vaginal *Lactobacilli* 3-fold compared to placebo.* This was accompanied by reduced incidence of placental insufficiency, pre-eclampsia and fetal distress in the probiotic supplemented women.

Anoshina TM, *et al. Perinatologiya I Pediatriya* 2016;4(68):22-25.

ASTARTE

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From the Publisher

➤ *continued from page 8*

The prion is a poorly understood organism that has been closely associated with causing mad cow disease (bovine spongiform encephalopathy [BSE]) and Creutzfeldt-Jakob disease. In wild cervid herds, the prion causes chronic wasting disease (CWD). Unlike mad cow disease, which is relatively rare, and Creutzfeldt-Jacob disease, which appears sporadically but historically in cultures that eat brain such as in Papua New Guinea, CWD has been spreading in herds throughout the Western US. There have been no clinical reports of humans acquiring CWD, but, in Canada, macaque monkeys fed infected meat did get CWD.[1]

Prion organisms build up in brain tissue by an unknown mechanism. The prion changes protein structures in the brain involved in synaptic transmission into an abnormal form; this transformation progresses rapidly converting much of the brain into the abnormal functioning protein. Before the disease progresses, there is a lengthy incubation period during which time the prion is thought to be replicating. Individual genetic variability causes greater or lesser susceptibility to prion infection. Human prion disease is not contagious. However, individuals handling human tissue with prion disease are at high risk for infection. Because prions accumulate in the brain and central nervous system, handling brain tissue poses the greatest risk. Nevertheless, all tissues in an infected animal or human contain prions. Medical sterilization techniques are not capable of destroying all prions; if a medical procedure is carried out on an individual with prion disease, all instrumentation is a bio-hazard and must be disposed.[2]

Is CWD prion disease a risk for hunters and their families? Venison and other game meat are thought to be much healthier than beef and pork because the animals are wild, not subject to industrialized livestock production. What about the individual who is already compromised immunologically with fibromyalgia, autoimmune disease, or cancer? If they eat prion-infected elk what happens to the prions they ingest?

Jade Teta, ND

When the patient comes into the exam room requesting a prescription for Viagra or Cialis, he is having erectile dysfunction (ED). Not uncommonly the next request is for testosterone or at least to be tested for testosterone deficiency. But what would be a comprehensive approach to assessing erectile dysfunction, and what are the options one should consider from both a naturopathic and functional medicine viewpoint? In this issue, Jade Teta, ND, examines the pathophysiology behind difficulty with erections and recommends appropriate lifestyle and treatment strategies. From a macronutrient viewpoint, zinc, magnesium, and vitamin D must be adequate in the diet. Exercise is definitely an important component in managing erectile dysfunction. Insulin resistance must be corrected, and metabolic syndrome as well as obesity need to be addressed. Of course, testosterone testing is a key component in assessing ED, but Teta advises consideration of

continued on page 12 ➤

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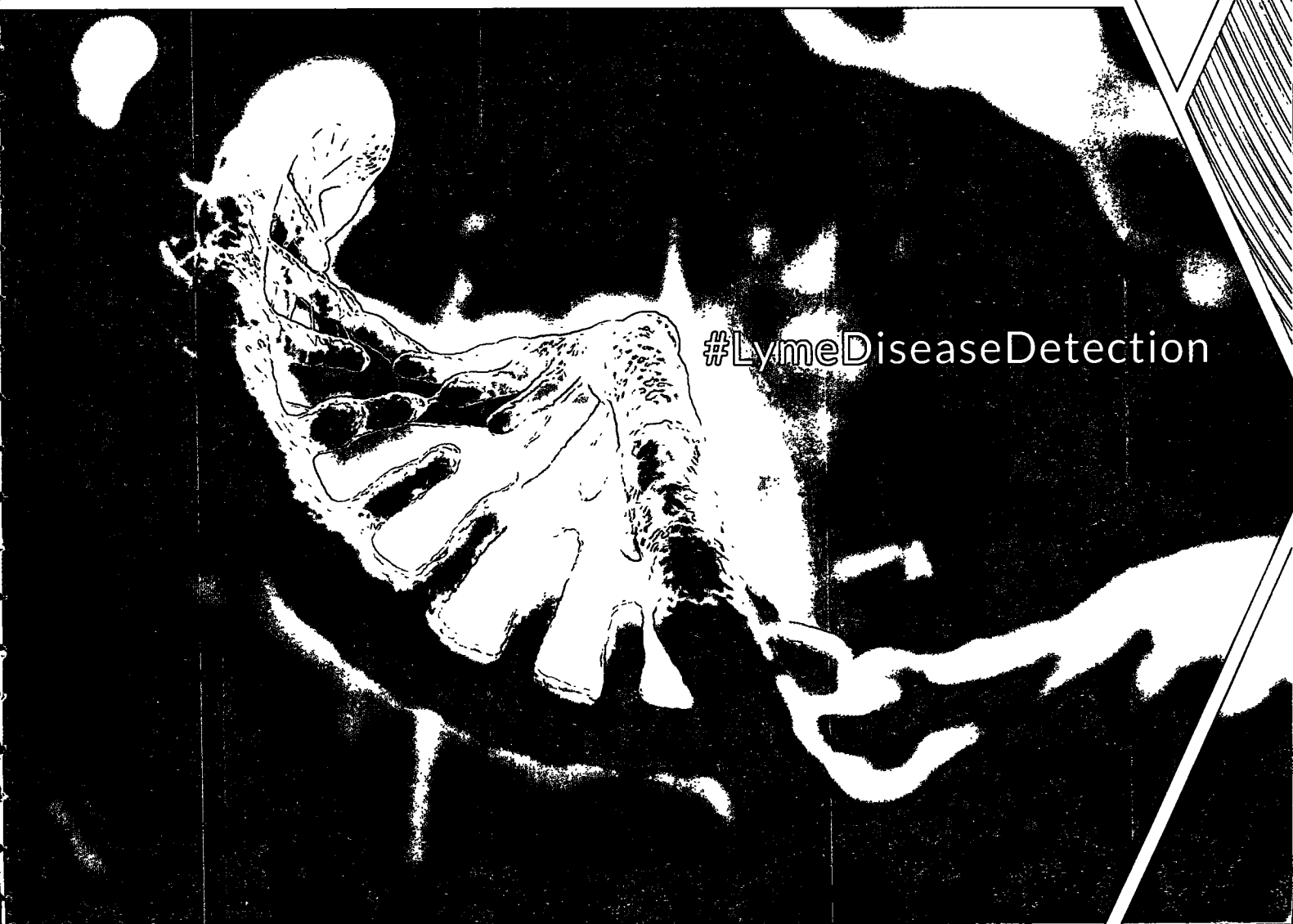

From the Publisher

➤ *continued from page 10*

both hormonal and non-hormonal strategies for increasing deficient testosterone.

Devaki Lindsey Berkson, MA, DC, CAN

As long as we are talking about male erectile dysfunction we should also consider female sexual dysfunctioning at the same time. While Dr. Devaki Lindsey Berkson does not discuss this in this issue, her book, *Sexy Brain: 10-Day Hormone Detox Program* details "How Sizzling Intimacy & Balanced Hormones Prevent Alzheimer's, Cancer, Depression and Divorce." Berkson is an expert on hormones and sexual dysfunction and has participated in research colloquiums because of her knowledge. Earlier books include the *Hormone Deception* (2000), *Natural Answers for Women's Health Questions* (2002), and *Safe Hormones, Smart Women* (2010). She participated in sharing her research at the Center for Environmental Research at Tulane University as a hormone scholar.

What Berkson details in *Sexy Brain* is how the hormone activity in men and women overlap but differ to a major degree. She explains that the major difference is how testosterone and estrogen alter our thinking and emotions. While estrogen makes women multi-task, it is their testosterone that grounds their thinking. Berkson argues that women acquire optimal levels of testosterone through heterosexual intercourse – the semen delivers testosterone that ultimately activates receptors far away in the brain's hippocampus. However, many women have unfulfilling sex because their hormone levels are deficient and imbalanced. She advises the need for bio-identical hormone replacement as well as non-hormonal approaches to balance hormone status. Once hormones are optimized, sexual functioning may still be impaired. Berkson provides a down-to-earth Kama Sutra for Western patients and doctors, explaining how the man should engage sexually – the foreplay, the touching, stimulating all the right spots, and achieving ultimate orgasms.

For those couples who are sexually dissatisfied, for those doctors who are dissatisfied, Berkson's *Sexy Brain* deserves a read. It would be a good one for the holidays.

Jean-Ronel Corbier, MD

If you are like me, the neurologists you refer to do a standard neurology workup, order CT scan or MRI (with contrast, please), nerve conduction studies, EEG, and rarely a spinal tap, then make a diagnosis. Medication and treatment is generally palliative, not restorative, and patients and caregivers now deal with managing their illness with the limited tools at hand. But what if there could be a restorative approach? What if the neurologist could move beyond the textbook diagnosis and the palliatives and consider restoration to optimal health? Of course, "the cure" for a disease is the objective of most neurologic societies, research associations, and patient advocacy groups, but until that cure is here, what next?

Jean-Ronel Corbier, MD, claims that we can "return optimal health" to many of these individuals through a "Restoration Model." Underlying restoration is a history of having sustained "physical, emotional, psychogenic, and spiritual" injury. Corbier argues that one must take the time to address each of these insults comprehensively, fastidiously uncovering each of them. And some insults may be very difficult to uncover and address, but Corbier emphasizes that the doctor and patient must be persistent in examining each of the insults despite their complexity. In the article in this issue Corbier explains how he uses the restoration model when he treats a youngster with autism, but he thinks it can be used in adult or child for all chronic disorders.

Dr. Corbier just presented at the International College of Integrative Medicine's October meeting in Grand Rapids, Michigan; for more information see icimed.com/conferences.

Dugald Seely, ND, MSc

This past September, Dr. Dugald Seely was awarded the Rogers Prize in Vancouver, British Columbia. It's not the Nobel Prize, but it's as prestigious an award for integrative and natural medicine. The prize is $250,000.00 but it is open only to Canadian physicians. Why don't we have a comparable integrative medicine prize in the US?

Our medical curmudgeon and Fellow of the American Board of Naturopathic Oncology (FABNO), Dr. Jacob Schor, offers an accolade of Dr. Seely and spells out why he richly deserves the award. Dr. Seely is a clinician and clinical researcher – he usually approaches his research in that order, first, clinical observation, and then evidence-based research. Dr. Seely's research has focused on oncology, but he has researched naturopathic treatment and cardiovascular disease, mental health, musculoskeletal disorders, and infectious disease. Just do a search of Dugald Seely on PubMed to get a sense of his research. To the medical nay-sayers who claim that naturopathic medicine is not evidence-based, Seely offers a potent dismissal of the skeptics' belittlement.

Dr. Seely and his MD brother were awarded a $3.85 million grant to study the adjunctive role of naturopathic medicine in the conventional treatment for lung, gastric, and esophageal cancer. The Thoracic-POISE study, "Thoracic Peri-Operative Integrative Surgical Care Evaluation," was started in 2014. As Dr. Schor reports, the study seeks to understand the role of naturopathic care before and after cancer surgery and also seeks to determine if such care reduces surgical adverse events and extends disease-free survival. The planned 11-year study will take place at multiple Canadian cancer centers coordinating with ND physicians.

Seely is the executive director of the Ottawa Integrative Cancer Centre; the clinic of 26 seeks to provide only evidenced-based complementary medicine. The *Townsend Letter* is very pleased to keynote Dugald Seely for his outstanding clinical work and research.

Jonathan Collin, MD

1. Davidson, A. The financial page: Pissed off. *The New Yorker*. 2017 Sept. 25; p. 41.
2. PDF Information about Prion disease, National Prion Clinic, University College London, Prion Clinic, prion.ucl.ac.uk

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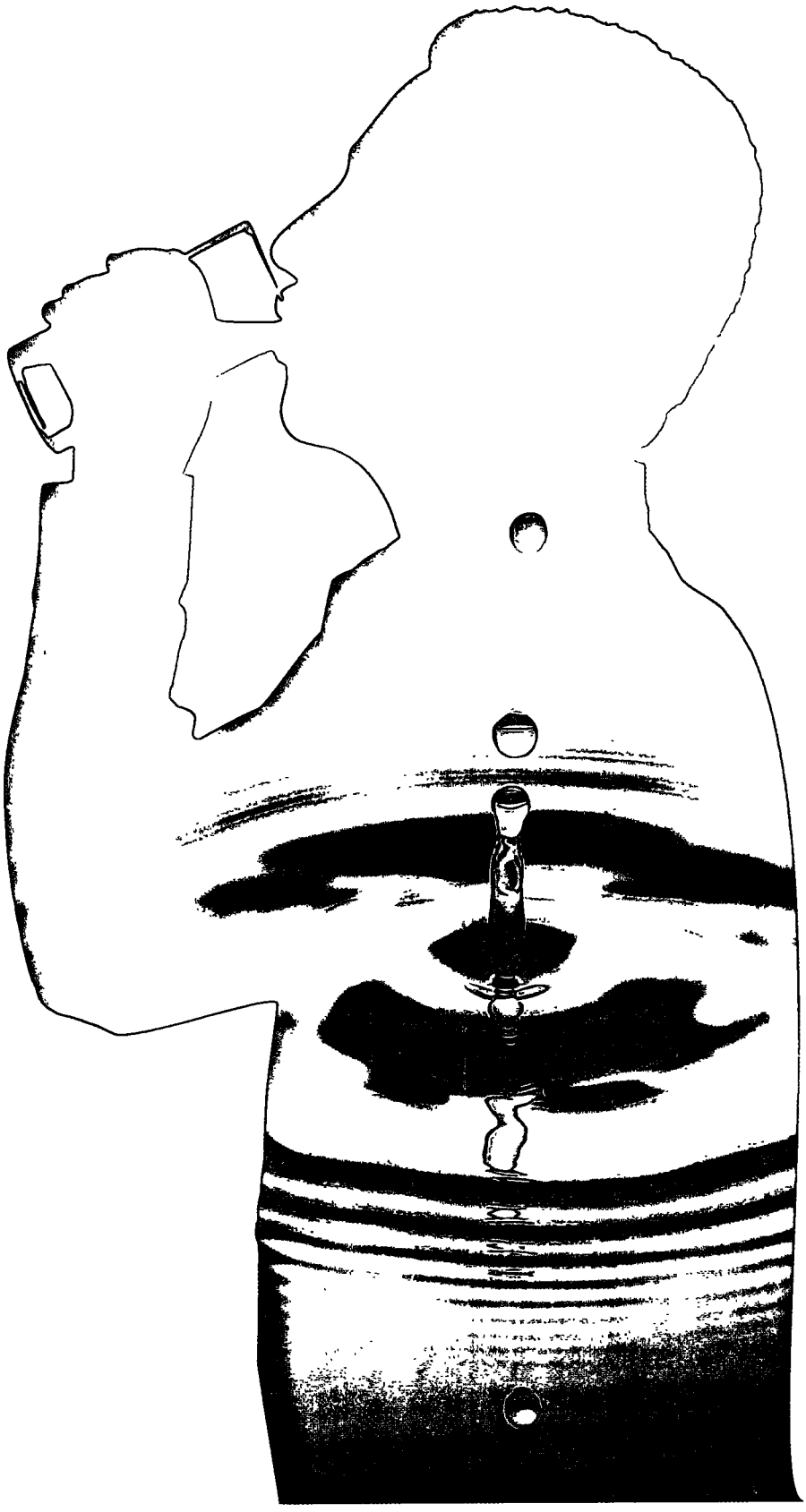

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briefed by Jule Klotter
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Sperm Count Decline

A 2017 systematic review and meta-regression analysis, conducted by an international group of researchers, reported a significant decline in sperm count among Western countries from 1973 to 2011. Hagai Levine and colleagues searched PubMed/MEDLINE and EMBASE for English-language studies, published 1981-2013, that used sperm concentration (SC) and/or total sperm count (TSC) to assess fertility in men. Studies involving men with infertility issues or exposure to environmental factors known to affect sperm count were excluded. Sperm motility and morphology were not part of the analysis because these factors were rarely included in older studies.

To perform the meta-regression analysis, Levine et al used 244 estimates of SC and TSC from 185 studies, involving a total of 42,935 men who had provided semen samples in 1973-2011. The researchers divided the 185 studies into two groups: one group included studies of men with known fertility (men who had fathered a baby), and the other consisted of studies that did not specifically select men with known fertility (usually involving young men in college or the military). The researchers also divided the data into two geographical groups: Western (North America, Europe, Australia, and New Zealand) and Other (South America, Asia, and Africa).

Overall, sperm concentration declined significantly between 1973 and 2011 (slope in unadjusted simple regression models -0.70 million/ml/year; 95% CI: -0.72 to -0.69; P< 0.001; slope in adjusted meta-regression models = -0.64; -1.06 to -0.22; P = 0.003). Semen volume did not significantly change during the study period. The decline was driven by data from the Western countries; South America, Asia, and Africa showed no significant declines, which was consistent with earlier studies. Western men unselected by fertility showed the greatest decrease; SC in this group declined 52.4% (-1.4% per year) and TSC declined 59.3% (-1.6% per year) over the four decades. Controlling for pre-selected variables (age, abstinence time, method of semen collection, methods of counting sperm, selection of population and study exclusion criteria, number of samples per man and completeness of data) had little affect on the slopes of decline. The researchers also performed an analysis of data collected from 1996-2011; this analysis showed no evidence that the decline was 'leveling off'. The researchers say that restricting their review to English language articles may have limited their results concerning non-Western countries.

"Declining mean SC implies that an increasing proportion of men have sperm counts below any given threshold for sub-fertility or infertility," write Levine et al. "The high proportion of men from Western countries with concentration below 40 million/ml is particularly concerning given the evidence that SC below this threshold is associated with a decreased monthly probability of conception." In addition to infertility, reduced sperm count is associated with overall morbidity and mortality. The authors say that environmental and lifestyle factors such as exposure to endocrine-disrupting chemicals (prenatally), pesticides, smoking, diet, and stress may be contributing to the decline. Levine et al state: "...a decline in sperm count might be considered as a 'canary in the coal mine' for male health across the lifespan. Our report of a continuing and robust decline should, therefore, trigger research into its causes, aiming for prevention."

Levine H, et al. Temporal trends in sperm count. a systematic review and meta-regression analysis. *Human Reproduction Update* 2017; 1-14.

Preventing Flu

Annual vaccination for influenza is viewed as the best preventive intervention available for an illness that can lead to pneumonia and other complications for at-risk individuals; yet, several articles in medical literature discuss the difficulty of creating an effective vaccine and point to gaps in our understanding of immunity. Because influenza viruses mutate rapidly (antigenic drift) and dominant strains can vary from year to year, people are advised to be vaccinated yearly with the newest vaccine. Yet, evidence indicates that yearly vaccination does not increase protection from flu.

John Treanor in his editorial commentary "Flu Vaccine – Too Much of a Good Thing?" says, "Over the last several years, many of these studies have suggested that vaccination in prior seasons can reduce the effectiveness of vaccination in the current season, a phenomenon first identified by Hoskins and colleagues in a British boarding school..." (Hoskins TW, et al.

Lancet. 1979;1:33-5). These studies led to the antigenic distance hypothesis, which posits that antigenically-similar vaccines given in two successive years cause the immune system to "... [focus] on the shared epitopes at the expense of novel epitopes on the second virus that might be important for the protection against a third, antigenically drifted virus."

A 2017 Canadian study from the Canadian Vaccine Effectiveness network found evidence that prior vaccination affects the response to current vaccination. This study, led by Danuta M. Skowronski, showed that vaccine effectiveness (VE) declined when the current vaccine was similar to the previous one and the circulating virus was a drift variant. When two successive vaccines were identical *and* a poor match for the circulating virus, as in the 2014-15 season, the effect of prior vaccination was "pronounced and statistically significant," according to Skowronski et al. Vaccine effectiveness for that year was 65%; but when that vaccine was given to people who had also been vaccinated the previous year, VE was -33%; they were more likely to get the flu.

Arnold S. Monto and colleagues at University of Michigan School of Public Health (Ann Arbor) point out that "...prior infection is more effective than vaccination in preventing subsequent infection, an observation that remains undisputed." In their review article, Monto et al refer to animal research in which ferrets *infected* with A(H3N2) virus displayed more protection against the lethal A(H5N1) virus than ferrets *vaccinated* with A(H3N2). Although animal research does not necessarily translate to human experience, Monto et al say, "...there is clearly a need to balance the prevention of severe influenza in young children, who are at high risk of complications, and the possible benefits of allowing the first infection in life to take place without modification by prior vaccination."

The observation that flu infection provides better protection than vaccination was supported by a 2011 Dutch study, led by Rogier Bodewes. Bodewes and Dutch colleagues compared virus-specific CD8 T cell immunity in 14 children with cystic fibrosis (mean age 6.2 years) who were vaccinated annually to CD8 T cell immunity in 27 unvaccinated children (mean age 5.9 years). The Netherlands recommends flu vaccination for children who are at high risk for complications but does not recommend universal vaccination for healthy children; so, the researchers did not have access to a group of healthy, vaccinated children for the study. Despite the difference in health status, the two groups of children had similar virus-specific CD4 T cell and antibody responses. However, only the unvaccinated group showed an age-dependent increase in virus-specific CD8 T cell response, as the children experienced infection. The authors say, "Our results indicate that annual influenza vaccination is effective against seasonal influenza but hampers the development of virus-specific CD8 T cell responses." CD8 T cells secret gamma-interferon against viruses and prevent unnecessary antibody formation. In addition, "...memory CD8 T cells provoked against seasonal influenza A viruses will cross-react with other influenza A viruses, even with those of other subtypes."

Are there ways to prevent flu and lessen its severity besides vaccination? A 2008 commentary by John J. Cannell and colleagues reported, "Vitamin D alone, whether from ultraviolet lamps, the sun, or from supplements, reduces the incidence of respiratory infections." This article cautions against using cod liver oil because today's products typically contain too much vitamin A and too little D.

A 2016 review reported that supplementation with the antioxidant vitamin C decreased pneumonia risk in people who were C-deficient but not in the well-nourished. Its use also decreased the time that patients with community-acquired pneumonia spent on mechanical ventilation. Vitamin C plays a role in regulating the lung's immune system.

Some botanicals also have anti-flu effects. James A. Duke, PhD, in his book *The Green Pharmacy* recommends elderberry, echinacea root, and fresh ginger root (in boiling water as a tea) for their anti-viral activity. Vaccination is just one, not the only, method for reducing risks from flu.

Bodewes R, et al. Annual Vaccination Against Influenza Virus Hampers Development of Virus-Specific CD8 T Cell Immunity in Children *Journal of Virology* November 2011: 11995-12000.

Cannell JJ, et al. Cod Liver Oil, Vitamin A Toxicity, Frequent Respiratory Infections, and the Vitamin D Deficiency Epidemic. *Annals of Otology, Rhinology & Laryngology.* 2008;117(11):864-870.

Li Y, Li G. Is Vitamin C Beneficial to patients with CAP? (abstract) *Curr Infect Dis Rep.* Aug 2016,18(8):24.

Monto AS, et al. The Doctrine of Original Antigenic Sin: Separating Food From Evil. *J Infect Dis.* June 15, 2017;215:1782-1788

Skowronski DM, et al. Serial vaccination and the antigen distance hypothesis. effects on influenza vaccine effectiveness during A(H3N2) epidemics in Canada, 2010-11 to 2014-15. *J Infect Dis.* 2017;215:1059-69

Treanor J. Flu Vaccine—Too Much of a Good Thing? *J Infect Dis* April 1, 2017;215.1017-1019.

Malnutrition and Aging

A Belgium research team conducted a systematic review of six high-quality, longitudinal studies that investigated risk factors for malnutrition in the older population. Malnutrition is associated with increased morbidity, mortality, and cost of care; yet, it is too often undetected or ignored. These studies assessed nutritional status using anthropometric measurements (body weight, BMI data) and/or nutritional screening tools that look at factors like loss of appetite, difficulty eating, weight loss, and mobility.

The variables that statistically correlated with the development of malnutrition between baseline and reassessment included frailty (for institutionalized people), excessive polypharmacy (defined as taking ≥ 10 drugs), functional decline, difficulty walking stairs (for persons under 75 years old), decline in cognitive capacity and dementia, Parkinson's disease, constipation, loss of over 5% of initial handgrip strength, and poor or moderate self-reported health status. Poor appetite, difficulty swallowing, and needing assistance to eat were other risk factors. Loss of interest in life among people living in institutions or communities was the only psychological factor linked to the development of malnutrition. Age, in itself, was not a risk factor for malnutrition, according to most of the reviewed studies.

The review also found three variables linked to better nutritional status: daily oral hygiene, sustained interest in life, and ability to eat unaided (community subjects). The reviewers comment, "Even in cases of adequate nutrient and energy intake, the nutritional status of older adults can be challenged by a compromised nutrient metabolism (such as absorption, distribution, storage, utilization, and excretion), drug-nutrient interactions, or altered nutrient needs."

While highlighting malnutrition in older populations is useful, using anthropometric measures and nutrition screening

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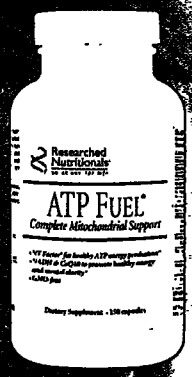

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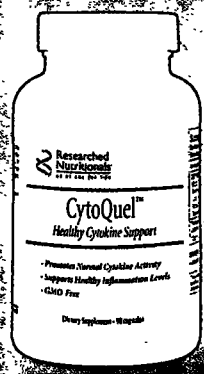

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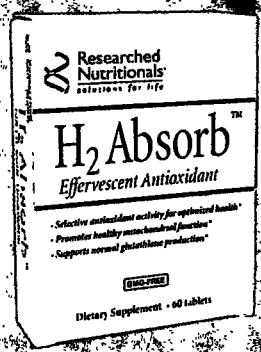

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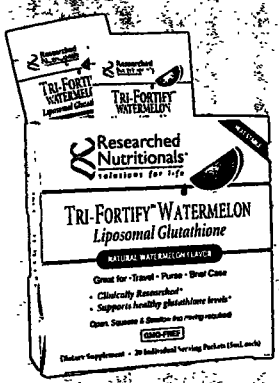

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ON THE COVER: Dugald Seely, ND, Awarded the Rogers Prize (pg. 34); Erectile Dysfunction, Lifestyle, and Testosterone (pg.40); Treating Mast Cell Activation Syndrome (pg. 50); *Helicobacter pylori* – Commensal or Pathogen? (pg. 71); Integrative Care for Myelofibrosis (pg. 56)

Shorts

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tools seem blunt instruments for assessing malnutrition to me. Ralph Campbell, MD, points out that common conditions, such as low energy or depression, memory loss, insomnia, reduced alertness, dry skin, and cold hands and feet can, themselves, indicate nutrient deficiencies that can be reversed with supplementation. "Rather than passing off these conditions as just being a product of ageing, how much better if would be to find more tangible causes....Supplements of essential nutrients such as vitamins and minerals including iodine taken in adequate doses can prevent or reverse many of the symptoms associated with age."

Campbell R. Much More Than "Ageing." Orthomolecular Medicine News Service. July 17, 2017.
Fávaro-Moreira NC, et al. Risk Factors for Malnutrition in Older Adults: A Systematic Review of the Literature Based on Longitudinal Data. *Adv Nutr*. 2016,7:507-22.

Mind-Body Interventions Change Gene Expression

Mind-body interventions (MBI), such as mindfulness, yoga, Tai Chi, Qigong, breath regulation, and relaxation response exercises, downregulate the nuclear factor kappa B (NF-κB) pathway, according to a 2017 review by Ivana Buric and colleagues: "...this is the opposite of the effects of chronic stress on gene expression and suggests that MBI practices may lead to a reduced risk of inflammation-related diseases." NF-κB is produced when stress activates the sympathetic nervous system. It activates the expression of genes responsible for inflammatory cytokine production: "Lower activity of NF-κB suggests reduced inflammation."

Buric et al found 18 studies in PubMed (through September 2016) that investigated mind-body practices using gene expression analysis. Eighty-one percent found statistically significant downregulation in the NF-κB pathway with MBI use. Two uncontrolled studies that found no change in gene-expression had small sample sizes (ten participants and two participants), inadequate for providing statistical power. The third study used a different method for detecting gene expression; the others used the TELiS bioinformatics analysis.

Biological inflammation markers were not affected as quickly as gene expression: "...the studies that employed circulating proteins (eg, CRP, interleukins, or cortisol) generally did not find significant results." Buric et al note that the two studies that controlled for practice frequency found some significant biological results when people who used MBI regularly were analyzed separately. Also, most of the reviewed studies lasted for no more than three months. While gene expression changes after a few weeks or less, circulating biological proteins did not.

The review authors say, "Although the studies reviewed here provide preliminary evidence that MBIs are associated with a reduced risk of inflammation-related diseases, it is unclear whether they are more effective than a range of lifestyle changes commonly recommended as a part of healthy lifestyle, such as regular exercise and a Mediterranean diet."

Buric I, et al. What Is the Molecular Signature of Mind-Body Interventions? A Systematic Review of Gene Expression Changes Induced by meditation and Related Practices *Front Immunol*. June 2017; 8:670.

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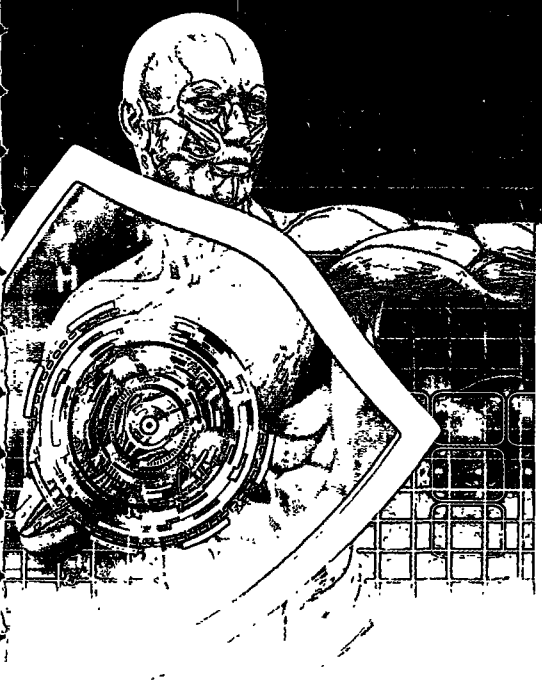

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Literature Review & Commentary

by Alan R. Gaby, MD
drgaby@earthlink.net

Omega-3 Fatty Acid Improves Outcomes in Acute Coronary Syndrome

Two hundred forty-one patients with acute coronary syndrome (myocardial infarction or unstable angina) were randomly assigned to receive 2 mg per day of pitavastatin with or without (control group) 1800 mg per day of eicosapentaenoic acid (EPA), begun within 24 hours after percutaneous coronary intervention. The primary endpoint was cardiovascular events occurring within one year, including death from a cardiovascular cause, nonfatal stroke, nonfatal myocardial infarction, and revascularization. The incidence of the primary endpoint was 54% lower (9.2% vs. 20.2%; p = 0.02) and cardiovascular disease-related mortality was 81% lower (0.8% vs. 4.2%; p = 0.04) in the EPA group than in the control group.

Comment: The results of this study indicate that the addition of EPA to a statin drug, as compared with a statin drug alone, decreased the incidence of cardiovascular events after percutaneous coronary intervention in patients with acute coronary syndrome. Possible mechanisms by which EPA was beneficial include an anti-inflammatory effect and inhibition of platelet aggregation.

Nosaka K, et al. Early initiation of eicosapentaenoic acid and statin treatment is associated with better clinical outcomes than statin alone in patients with acute coronary syndromes: 1-year outcomes of a randomized controlled study. *Int J Cardiol.* 2017;228:173-179.

Disaccharidase Deficiencies in Children with Chronic Abdominal Pain

Of 203 children (mean age, 11.5 years) with chronic abdominal pain who presented to the gastroenterology clinic at Children's Hospital of Wisconsin, the proportion with abnormally low disaccharidase levels in small-intestinal biopsy samples was 37% for lactase, 21% for sucrase, 25% for glucoamylase (which cleaves glucose from maltose or starch), and 8% for palatinase (sucrase-isomaltase). Thirty-nine percent of the children with low lactase also had low sucrase, and 67% of those with low sucrase also had low lactase.

Comment: Lactose, sucrose, maltose, and isomaltose are the major disaccharides present in the human diet. These non-absorbable disaccharides are hydrolyzed to absorbable monosaccharides by disaccharidase enzymes present in the small-intestinal mucosa. It is well known that malabsorbed lactose is fermented by intestinal bacteria, which leads to the production of gases that can cause various gastrointestinal symptoms. Individuals with lactase deficiency often experience an improvement in various gastrointestinal symptoms when they avoid cow's milk and other lactose-containing foods. Similarly, people with congenital sucrase deficiency experience an improvement in gastrointestinal symptoms when they avoid sucrose-containing foods.

In the present study, disaccharidase deficiencies were found to be common in children with chronic abdominal pain. In lieu of a small-bowel biopsy, a therapeutic trial of restricting dietary intake of lactose, sucrose, maltose, and isomaltose may relieve symptoms in some cases. After clinical improvement occurs, gradual reintroduction of disaccharides might help the patient determine which disaccharides they can tolerate and at what level of intake. Information on how to consume a low-disaccharide diet is available on the Internet.[1]

El-Chammas K, et al. Disaccharidase deficiencies in children with chronic abdominal pain. *JPEN J Parenter Enteral Nutr.* 2017;41:463-469.

Does Too Much Folic Acid or Vitamin B12 Cause Autism?

The Boston Birth cohort is a longitudinal prospective cohort study of 1,391 low-income urban, primarily minority mother-child pairs at the Boston Medical Center. Maternal multivitamin

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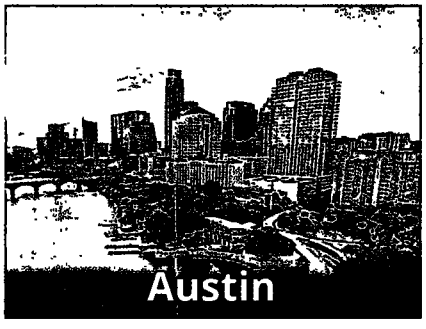

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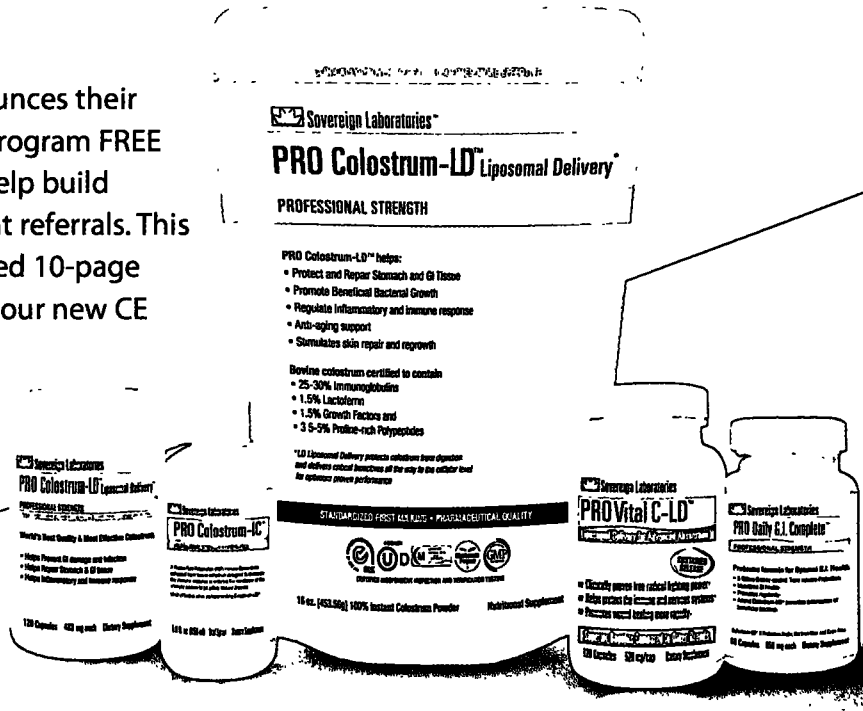

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Gaby's Literature Review

➤ *continued from page 20*

supplementation (3 to 5 times a week) was associated with a significantly lower risk of autism spectrum disorder (ASD) across all trimesters (adjusted hazard ratio [HR] = 0.33, 0.38, and 0.43 for 1st, 2nd, and 3rd trimesters, respectively). However, high levels of maternal plasma folate (> 59 nmol/L; HR = 2.27; p = 0.007) and vitamin B12 (> 600 pmol/L; HR = 3.01; p = 0.001) were associated with an increased risk of ASD. The greatest risk was in children of mothers who had high levels of both folate and vitamin B12 (HR = 17.6; p < 0.001).

Comment: A superficial interpretation of this research might be that taking a multivitamin during pregnancy can prevent ASD, but that taking too much folic acid or vitamin B12 can increase the risk of developing ASD. This study was widely reported in the media, and many reporters concluded that taking a lot of folic acid or vitamin B12 during pregnancy may be harmful. However, the study was observational and therefore cannot prove causation. Unfortunately, neither the original study nor the media reports provided any data (or even any speculation) on what dosages of these vitamins are beneficial and what dosages are harmful. One wonders how many pregnant women were frightened out of taking their multivitamin out of fear that it might contain too much folic acid or vitamin B12.

The likelihood is that the adverse associations reported in this study are spurious and do not imply a deleterious effect of folic acid or vitamin B12. The presence of a high serum folate concentration in a person who is not taking large doses of folic acid is a marker for small-intestinal bacterial overgrowth (SIBO), because some organisms that colonize the small intestine are capable of synthesizing folates.[2,3] SIBO can cause deficiencies of many different nutrients, which could increase the risk of abnormal fetal brain development. Thus, high folate levels may be associated with an increased risk of ASD not because of any adverse effect of folate, but because of the association of high folate levels with SIBO. Similarly, an elevated vitamin B12 level is seen in people with liver disease,[4] and even subtle liver dysfunction during pregnancy has the potential to cause adverse outcomes in the child.

Folic acid supplementation during pregnancy has clearly been shown to prevent neural tube defects. For women who have had a previous child with a neural tube defect, the Centers for Disease Control and Prevention (CDC) recommends a relatively large dose of folic acid (4,000 µg per day). Nothing about the present study should dissuade these women from following the CDC guidelines.

Raghavan R, et al. Maternal plasma folate, vitamin B12 levels and multivitamin supplementation during pregnancy and risk of autism spectrum disorder in the Boston Birth Cohort. Experimental Biology 2016 Meeting.

Does Exposure to Phthalates Promote Uterine Fibroids and Endometriosis?

Myometrial and leiomyoma (uterine fibroid) cells obtained from women with uterine fibroids were exposed to di-(2-ethylhexyl)-phthalate (DEHP) *in vitro*. Exposure to DEHP led to increased viability and increased expression of proliferating cell nuclear antigen and type I collagen in myometrial and leiomyoma cells. The urinary concentration of mono-(2-ethyl-5-carboxypentyl) phthalate was higher (p < 0.03) in women with uterine fibroids than in controls who had undergone a uterine surgical procedure but who did not have fibroids.

In another report, exposure of endometrial cells to DEHP *in vitro* increased their proliferative activity. Oral administration of DEHP to mice that had been subjected to implantation of human endometrial tissue significantly increased the size of the endometrial implant. In a case-control study, the mean urinary concentrations of mono (2-ethyl-5-hydroxyhexyl) phthalate, mono (2-ethyl-5-oxohexyl) phthalate, and mono (2-ethyl-5-carboxyphentyl) phthalate were significantly higher in women with endometriosis than in controls.

Comment: Phthalates are endocrine-disrupting chemicals that are widely used in plastics (including food wrappers), makeup, shampoo, soaps, paints, medical products, and some pesticides. Phthalate metabolites are detectable in more than 75% of people in the US. The results of the studies described above suggest that phthalate exposure may contribute to the pathogenesis of uterine fibroids and endometriosis.

Kim JH, et al. In vitro effects of phthalate esters in human myometrial and leiomyoma cells and increased urinary level of phthalate metabolite in women with uterine leiomyoma. *Fertil Steril.* 2017;107:1061-1069.e1.

Kim SH, et al. Possible role of phthalate in the pathogenesis of endometriosis: in vitro, animal, and human data. *J Clin Endocrinol Metab.* 2015;100:E1502-E1511.

Folic Acid and Psoriasis

The association between methylenetetrahydrofolate reductase (MTHFR) polymorphisms C677T and A1298C and psoriasis risk was investigated in 84 Turkish patients with psoriasis and 212 healthy controls. The frequency of both the MTHFR 677TT and A1298C (homozygous) genotypes was markedly higher in patients than in controls. The T allele of MTHFR 677 and the C allele of MTHFR 1298 were associated with a 12.4-fold and a 17.0-fold increase, respectively, in the risk of having psoriasis.

Comment: This study found strong associations between polymorphisms of the gene that encodes for MTHFR and the risk of having psoriasis. Other research in this area has been conflicting, ranging from the same strong association found in the present study to no association. MTHFR is involved in folate metabolism. If there are indeed abnormalities of folate metabolism in some patients with psoriasis, that might explain the clinical observation that administration of large doses of folic acid improves or resolves the skin lesions in many patients with psoriasis.

One practitioner treated 40 psoriatic patients with high-dose folic acid (usually 100 mg per day) in combination with 1,000 mg per day of vitamin C. About 60% of the patients had complete or near-complete resolution of lesions and an additional 20% had lesser degrees of improvement. Improvement was typically noticeable after one month, and the maximum level of improvement was seen after an average of 2.5 months. After the maximum level of improvement was achieved, patients usually received a maintenance dose of 25 mg per day of folic acid.[5]

Kilic S, et al. Possible association between germline methylenetetrahydrofolate reductase gene polymorphisms and psoriasis risk in a Turkish population. *Clin Exp Dermatol.* 2017;42:8-13.

Vitamin C Benefits Dialysis Patients

Twenty-two patients with chronic renal failure who were receiving maintenance hemodialysis and who had functional iron deficiency (defined as transferrin saturation < 30 % and ferritin > 100 µg/L) and erythropoietin requirements of at least 4000 IU per hemodialysis session received oral vitamin C (250 mg per day) for three months. Iron supplements were not given. Among the 15 patients who completed the study, the median erythropoietin dose requirement fell by 15% ($p = 0.01$) and the mean hemoglobin concentration increased from 10.1 g/dl to 10.7 g/dl ($p = 0.03$). Among the seven patients who had a decrease in their erythropoietin dose requirement, the mean decrease was 33%.

Comment: Functional iron deficiency is a major cause of persistent anemia in dialysis patients and also contributes to a suboptimal response to erythropoietin. Vitamin C enhances the mobilization of iron and increases its bioavailability. In previous studies, high-dose intravenous vitamin C decreased erythropoietin requirements and improved hemoglobin levels. The results of the present study suggest that a relatively low dose of oral vitamin C can also reduce erythropoietin requirements. In patients with renal failure, large doses of vitamin C can increase the deposition of oxalate in soft tissues, with potentially serious consequences. Low-dose vitamin C is therefore preferable to high-dose vitamin C in such patients. Erythropoietin is an expensive drug, so any low-cost treatment that can decrease erythropoietin requirements would reduce the overall cost of treatment in patients on hemodialysis.

Sultana T, et al. Oral vitamin C supplementation reduces erythropoietin requirement in hemodialysis patients with functional iron deficiency. *Int Urol Nephrol*.2016;48:1519-1524.

Levothyroxine: A Less-Than-Optimal Treatment for Hypothyroidism

A cross-sectional study was conducted on 9,981 participants in the US National Health and Nutrition Examination Survey (2001-2012) who had normal TSH levels. Participants using levothyroxine were compared with controls matched for age, sex, race, and serum TSH. The mean serum concentrations of total T4 (9.14 vs. 8.08 µg/dl) and free T4 (0.94 v. 0.80 ng/ml) were significantly higher, and the mean serum concentrations of total T3 (97.6 vs. 108.3 ng/ml) and free T3 (2.85 vs. 3.01 pg/ml) were significantly lower in people taking levothyroxine than in controls. Compared with controls, participants taking levothyroxine had a 15-20% lower mean serum T3:T4 ratio. Mean TSH levels were similar between groups. Compared with controls, levothyroxine-treated participants had higher body mass index ($p < 0.001$) despite consuming fewer calories per kg of body weight, and were more likely to be taking beta-blockers ($p < 0.0001$), statins ($p < 0.01$), and antidepressants ($p < 0.01$).

Comment: These results indicate that people taking levothyroxine, as compared with matched controls, had lower serum T3:T4 ratios and had certain features consistent with possible hypothyroidism, despite having normal TSH levels. While the human thyroid gland secretes both levothyroxine and triiodothyronine (T3), the conventional approach to treating hypothyroidism is to administer levothyroxine by itself. The assumption upon which this approach is based is that the body converts levothyroxine to triiodothyronine in the exact amounts that are needed. The altered T3:T4 ratio seen in this study in levothyroxine-treated patients suggests that this assumption is not correct. Previous research and extensive clinical experience suggest that preparations containing both levothyroxine and triiodothyronine are more effective than levothyroxine alone for many hypothyroid patients.

Peterson SJ, et al. Is a normal TSH synonymous with "euthyroidism" in levothyroxine monotherapy? *J Clin Endocrinol Metab*. 2016;101:4964-4973.

Vitamin D in Heart Failure: Mixed Results

Two hundred twenty-nine patients (mean age, 69 years) with heart failure (New York Heart Association class II or III), a left ventricular ejection fraction (LVEF) of 45% or lower (mean, 26.1%), and a serum 25-hydroxyvitamin D level below 20 ng/ml (mean, 14.9 ng/ml) were randomly assigned to receive, in double-blind fashion, 4,000 IU per day of vitamin D_3 or placebo for one year. The primary endpoint was the change in six-minute walk distance between baseline and 12 months. The mean six-minute walk distance decreased by 12.6 meters in the vitamin D group and increased by 10.1 meters in the placebo group ($p = 0.26$ for the difference in the change between groups). Mean LVEF (a secondary endpoint) increased by 7.65% in the vitamin D group and by 1.36% in the placebo group ($p < 0.0001$ for the difference in the change between groups). In addition, compared with placebo, vitamin D resulted in a significant reversal of left ventricular remodeling (a secondary endpoint; indicating an improvement in left ventricular structure).

Comment: In this study of patients with heart failure and low 25-hydroxyvitamin D levels, vitamin D supplementation for one year resulted in a trend toward worse aerobic capacity but a significant improvement in physiological parameters (LVEF and left ventricular structure). Thus, the overall effect of vitamin D in this patient population is unclear. Longer-term studies may be needed to determine the effect of vitamin D supplementation on more clinically important endpoints such as mortality and frequency of hospitalization.

Witte KK, et al. Effects of vitamin D on cardiac function in patients with chronic HF: The VINDICATE study. *J Am Coll Cardiol*. 2016;67:2593-2603.

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Silver Hydrosol – Nature's Best Kept Health Secret

by Rob MacCuspie, PhD

Historical Uses of Silver

Silver has been used throughout history to improve human health. The ancient Romans, Greeks, Egyptians, and Phoenicians used silver vessels to preserve their drinking water.[1] Hippocrates, the father of modern medicine, was the first to describe the antimicrobial benefits of silver.[2] In the Middle Ages, silver eating utensils gave rise to the phrase "born with a silver spoon in your mouth." Silver found use in antimicrobial and wound-healing applications for battlefield medicine in the 1800s and early 1900s.[3] Today, silver is used to purify drinking water on the international space station,[4] promote wound healing,[5] and in medical devices.[6]

Silver is a naturally-occurring element found in many places, from drinking water to foods, including mammalian milk, wheat, and mushrooms. One study conducted in the United Kingdom found that the average adult consumes 27 micrograms of silver in their daily diet (Table 1).[7]

Peer-reviewed literature provides evidence of naturally occurring silver colloids (silver nanoparticles) in river waters in Texas[12] and Mexico,[13] with the mechanisms of particle formation being understood to include the natural organic matter found in freshwaters.[14] Natural silver nanomaterials have been present throughout history, and pose no health risks as opposed to engineered nanomaterials that can cause concerns.

Table 1

Food Source	Silver Concentration	Average Daily Consumption	Average Daily Silver Intake
Refined wheat flour[8]	0.3 µg/g	164 g	49 µg
Wheat bran[9]	0.9 µg/g	10.1 g	9.1 µg
Milk[10]	27-54 µg/L	1 x 8oz glass (adult)	11 µg
Milk[10]	Avg. 47 µg/L	3 x 8oz glass (2yo)	33 µg
Mushrooms[11]	1.7 – 110 µg/g	3 oz. serving	0.14-9.4 µg/serving
Total Diet, UK[7]			27 +/- 17 µg

Table 2

in vivo Toxicology Study	No Observed Adverse Event*?	# of times EPA daily RfD of 5 µg/kg	mg silver / kg body weight	tsp/day, @23ppm
1 tsp of 23ppm Silver Hydrosol	☑	0.33	0.01	1
Morishita, et al., 2016, "low" dose[18]	☑	300	1.5	913
Xue, et al., 2012, "low" dose[19]	☑	1,500	7.5	4,565
Loeschner, et al., 2011, "low" dose[20]	☑	1,860	9.3	5,661
Wilding, et al., 2016[16]	☑	2,000	10	6,087
Morishita, et al., 2016, "high" dose[18]	☑	2,000	10	6,087
Loeschner, et al., 2011, "high" dose[20]	☑	2,520	12.6	7,670
Kim, et al., 2008, "low" dose[21]	☑	6,000	30	18,261
Xue, et al., 2012, "mid" dose[19]	☑	6,000	30	18,261
Xue, et al., 2012, "high" dose[19]	lung & liver inflammation	24,000	120	73,043
Kim, et al., 2008, "high" dose[21]	elevated liver enzymes	60,000	300	182,609

**These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure, or prevent disease.*

Safety of Silver

Numerous peer-reviewed *in vivo* studies have been conducted to evaluate the potential for silver nanoparticles to have acute or chronic toxicity effects. Table 2 summarizes some of these results. Dosages are presented in terms of mg/kg/day, as well as the number of times in excess of the US EPA's recommended oral daily reference dose (RfD) to ensure safety in drinking water. Argyria has been reported when silver exposure to the body in any form (i.e., metal, ionic or nanoparticle), either orally or by inhalation, exceeds a lifetime 10 gram exposure.[15] A conversion to the number of tsp of a 23 ppm silver product required to achieve an equivalent silver mass dose is also provided. No observed adverse events were reported at 6,000X the RfD. For context, 18,261 tsp is almost 24 gallons. Consuming that volume of water would pose a health hazard long before the quantity of silver would.

It is critical to keep in mind that the silvers in these studies were of highest purity standards (e.g., pharmaceutical grade water). Safety profiles of colloidal silvers can differ dramatically when impurities or other formulation

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Silver Hydrosol

➤ *continued from page 26*

ingredients are present. It is generally accepted that only high purity products, such as silver hydrosol with only two ingredients, can use the current peer-reviewed literature as guidance. The lack of bioavailability found in colloidal silver with large particles arises from the lack of surface area, leading to exponentially lower efficacy as size increases. This is visible to the eye as yellow, brown, or orange colors due to the surface plasmon resonance of silver nanoparticles.

Peer-reviewed research indicates that particle size, silver purity, the purity of the water, and the purity of the colloidal silver formulation are important when assessing the safety of silver products. Silver hydrosols only contain bioactive silver ions and naturally occurring nanoparticles. Look for a product that uses only pharmaceutical grade purified water, and 99.999% pure silver to ensure safety.*

Silver and the Gut Microbiome

A 2016 peer-reviewed study from University of Michigan has explored the potential for impact of silver oral dietary supplementation affecting the gut microbiome.[16] The study revealed that compared to water controls, silver did not significantly affect the biodiversity of species in the gut microbiome. However, a prescription antibiotic affected the balance of species by over 50%. This is consistent with the understanding of gastrointestinal distress when taking prescription antibiotics and the common recommendations to take probiotics during such treatments.

Remarkably, silver has no disruption on the gut microbiome diversity. Furthermore, the excretion profile of silver was found to follow a bell-shaped curve time profile, with over 98% excretion through fecal elimination after 24 hours.[17]

Practical Applications

Silver hydrosol dietary supplementation can be used to provide daily immune support.* For short term situations, multiple doses per day can provide additional support when needed.* Silver, along with basic immune support, has been used historically to support skin, gut, oral and eye health.[2]

Silver first aid gels can provide a natural alternative for individuals seeking non-pharmaceutical choices. Silver first aid gels will follow the same efficacy trends as liquid dietary supplements.* Clear and colorless products indicate maximum bioactivity, while yellow color is an indication of the presence of colloidal silver particles, acting as inactive silver metal reservoirs.

High quality and purity products ensure that the margin of safety identified in recent literature is transferred seamlessly to patients utilizing one of nature's best kept health secrets.

**These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure, or prevent disease.*

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Rob MacCuspie, PhD, is the Director of Science at Natural Immunogenics. His nearly twenty years of experience spans government national labs, academia, and industry. Career highlights include leading the development of the silver nanoparticle reference materials for the National Institute of Standards and Technology, publishing over 40 peer-reviewed papers and one US patent.

"Dr. Rob" began his journey to integrative medicine through his wife's health journey. An integrative practitioner used gene and antibody tests to diagnose her condition when allopathic medicine had failed for years. As part of her diet changes and supplement regimen, the practitioner recommended silver hydrosol to support her immune system. Dr. Rob is excited to now be able to help others discover the health benefits of silver he has learned in his professional and personal experiences.

MitoQ®: A Highly Bioavailable, Mitochondria-Targeted Form of Coenzyme Q10

by Chris D. Meletis, ND, Susanne Bennett, DC, and Kimberly Wilkes

Tiny organelles known as mitochondria are the body's equivalent of the batteries that power electrical devices. In other words, they are responsible for charging cells through the production of adenosine triphosphate (ATP), the energy molecule produced via the mitochondria's electron transport chain. Any factor that impairs mitochondrial function and disrupts the production of ATP can lead to fatigue, pain and inflammation as well as a significant number of diseases. For example, aging,[1-4] chronic stress,[5,6] certain pharmaceutical drugs,[7] ingesting high-fructose corn syrup,[8] environmental toxins such as heavy metals[9] and air pollution,[10] even the herbicides sprayed on food[11,12] have all been found to impair mitochondrial function. In fact, in today's world, the mitochondria have a lot going against them.

The antioxidant coenzyme Q10 (CoQ10) is well known for its role in mitochondrial function. The overproduction of reactive oxygen species (ROS) by mitochondria is responsible for mitochondrial impairment and plays a major role in many diseases. Mitochondrial damage can be mitigated by improving mitochondrial antioxidant capacity through supplementing with ROS scavenger CoQ10, as it plays a critical role in the energy-producing electron transport chain. Known for its mitochondrial-enhancing properties, CoQ10 has been shown to lower mortality and increase exercise capacity in heart failure patients,[13] diminish the frequency, duration, and severity of migraines,[14] reduce wrinkles and improve smoothness of skin,[15] and improve endothelial function and muscle recovery after strenuous exercise.[16] CoQ10 is designed to sit in the inner mitochondrial membrane and does not cross cellular or mitochondrial membranes easily. For that reason, mitochondria manufacture CoQ10 inside the inner membrane and this is why the effectiveness of exogenous CoQ10 is significantly limited by its inability to reach the mitochondria.

In this article, we will discuss the role of CoQ10 in supporting mitochondrial function in various diseases with a special emphasis on a new mitochondria-targeted form of CoQ10 known as MitoQ (mitoquinol). Drs. Meletis and Bennett use this form of CoQ10 in their clinical practices, with much success.

Enhancing the Bioavailability of CoQ10

Because of its lipophilic properties, large molecular weight, and differences in its gastrointestinal permeability, CoQ10 has low oral bioavailability and only a small amount of oral CoQ10 finds its way to the circulatory system.[17] Intracellular delivery is also a challenge and only a small percentage of the absorbed CoQ10 is available to the mitochondria.[17] An analysis of several studies indicates that high doses of CoQ10 supplementation for a prolonged period of time are needed to elevate CoQ10 tissue levels.[18] Additionally, the increase of CoQ10 that occurs after supplementation varies in different tissues.[18]

Many methods have been investigated to optimize CoQ10's ability to enter tissues and mitochondria including reducing particle size, creating emulsification and phospholipid delivery systems, with limited success.[17] MitoQ researchers finally achieved success in enhancing the delivery of CoQ10 into the mitochondria when they attached the ubiquinol form of CoQ10 to the lipophilic triphenylphosphonium cation, which allowed CoQ10 to enter into the mitochondria driven by the large mitochondrial membrane potential.[19]

This combination of ubiquinol and the triphenylphosphonium cation, known as mitoquinol, or MitoQ for short, is positively charged. Through an electrical gradient, MitoQ is attracted to the negatively charged interior of the cell, passing through the cell's plasma membrane and ultimately penetrating the mitochondria's double membrane. Lipophilic cations like triphenylphosphonium are easily able to penetrate lipid bilayers because they possess a charge that is distributed over a large surface region and the potential gradient allows them to accumulate in the mitochondrial matrix.[20,21]

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MitoQ is transported rapidly into isolated mitochondria. Inside the mitochondria virtually all of the acquired MitoQ is adsorbed to the matrix surface of the inner membrane.[22] This ability of MitoQ to enter the inner membrane of the mitochondria substantially improves CoQ10's antioxidant capacity.[22] MitoQ accumulates inside the mitochondria at concentrations up to a thousandfold greater than outside the cell.[23] MitoQ is especially effective at delivering CoQ10 into tissues with high-energy needs where greater numbers of mitochondria are concentrated including neurons, cardiac muscle, and the liver and kidneys.[22,23]

Unlike many other forms of CoQ10, MitoQ is water soluble and demonstrates optimal oral bioavailability. Peak plasma levels are achieved in less than an hour.[24] MitoQ is able to quickly penetrate all biological membranes, including the blood-brain barrier.[25]

The effects of MitoQ are probably attributed to accumulation of the ubiquinol form of CoQ10.[26] After the ubiquinol form of MitoQ quenches a free radical, it is oxidized to ubiquinone. Soon after, Complex II recycles the ubiquinone back to ubiquinol, which is a more powerful antioxidant.[26] Ubiquinol is highly effective at suppressing lipid peroxidation in phospholipid bilayers.[27] Due to its recycling back to ubiquinol, MitoQ is especially effective against lipid peroxidation but can also reduce peroxynitrite and superoxide radicals.[26]

Potential Applications for Mitochondria-Targeted CoQ10

MitoQ has been extensively evaluated in preclinical studies and several human trials were conducted, with more on the way. The following is a brief review of the evidence for MitoQ's effectiveness.

Liver Health

Hepatocytes (liver cells) have a high concentration of mitochondria and therefore benefit from antioxidant protection. One of the first clinical trials to be conducted on MitoQ investigated its effects in patients with the hepatitis C virus (HCV).[28] Increased oxidative stress and the ensuing mitochondrial damage are mechanisms responsible for the liver injury that occurs in chronic HCV infection. Inhibiting mitochondrial oxidative damage may therefore be beneficial. Consequently, researchers conducted a phase II study to determine the effect of MitoQ on serum aminotransferases and HCV RNA levels in patients with HCV. The study authors randomized 30 HCV patients who either did not respond to standard therapy or were unsuitable for standard-of-care to receive MitoQ (40 mg or 80 mg) or placebo once daily for 28 days. Patients receiving either dose of MitoQ experienced pronounced declines in absolute and percentage changes in serum alanine transaminase (ALT) from baseline to treatment day 28. ALT is a significant indicator of liver damage and inflammation. MitoQ did not affect HCV load.

MitoQ has also been studied for its supportive role in cirrhosis. In this disease, activated hepatic stellate cells (HSC) are involved in increasing intrahepatic vascular resistance and the development of portal hypertension.[29] Cirrhosis is also associated with elevated reactive oxygen species in the liver, which may explain why antioxidants lower portal pressure.[29] Because much of this increased ROS production originates in the mitochondria, researchers tested MitoQ on HSC from human livers, as well as on liver cells from control and cirrhotic rats.[29] The researchers also conducted an in vivo experiment in rats in which the effects of 5 mg/kg/day of MitoQ for two weeks on oxidative stress, systemic and hepatic hemodynamics, liver fibrosis, HSC phenotype, and liver inflammation was compared to a control compound.[29] MitoQ inhibited the activity of human and rat HSC. Furthermore, in the rat model, MitoQ reduced hepatic oxidative stress, improved the HSC phenotype, decreased intrahepatic vascular resistance, and suppressed liver fibrosis. These effects were accompanied by a pronounced decline in portal pressure without changes in arterial pressure.

Fibromyalgia and Chronic Fatigue Syndrome

Fibromyalgia is a disorder characterized by widespread pain and tenderness along with other symptoms including fatigue, cognitive problems, and poor sleep. Approximately 2% to 8% of the population suffers from fibromyalgia.[30] Myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS) are similar disorders to fibromyalgia and are characterized by malaise after exertion and unexplained, chronic fatigue. Scientists investigated the effects of MitoQ on 100 patients with fibromyalgia, CFS, or ME.[31] The fibromyalgia patients taking MitoQ experienced significant declines in pain scores (up to 33%) while no change was observed in the placebo group. Furthermore, patients given MitoQ experienced a 13% increase in working memory. CFS/ME patients given MitoQ did not experience notable effects in a double blind trial, but significant improvements in pain, energy, sleep quality, and mental clarity were observed in a separate open-label arm of the experiment.[31]

Cognitive and Neurological Health

Alzheimer's disease is the most common neurodegenerative disease and an important cause of dementia among elderly individuals.[25] Research indicates that mitochondrial impairment and oxidative stress are involved in Alzheimer's disease progression.[25] Researchers studied whether MitoQ can suppress pathology similar to Alzheimer's in mouse cortical neurons in cell culture, and in a triple transgenic mouse model of Alzheimer's disease.[25] In the cortical neurons, MitoQ diminished the neurotoxicity caused by amyloid beta (peptides that accumulate in Alzheimer's-affected brains), stopped the elevated production of reactive species, and decreased the loss of mitochondrial membrane potential. MitoQ given to mice for five months stopped the development of Alzheimer's-like pathologies such as cognitive decline, oxidative stress, Aβ accumulation, astrogliosis, synaptic loss, and caspase activation in the brain.

MitoQ also has been studied in Parkinson's disease, a chronic neurodegenerative disorder associated with neuronal mitochondrial dysfunction and low concentrations of the neurotransmitter dopamine. In mice,

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mesencephalic neuronal cells, and cultured dopaminergic cells exposed to toxins, MitoQ prevented neurotoxicity.[32] In an in vitro model of Parkinson's disease, MitoQ inhibited mitochondrial fragmentation due to oxidative stress.[33] A phase II, double-blind study of MitoQ versus a placebo in 128 Parkinson's patients did not demonstrate any effect of MitoQ on disease progression.[34] This was likely due to the commencement of therapy when the neuronal injury was already too extensive to achieve any benefit from use of a neuroprotective agent. However, the study did demonstrate the excellent safety and tolerability of long-term use of MitoQ.

Maintaining Healthy Weight

Animal studies suggest MitoQ can protect against the effects of a high-fat diet. Mice prone to obesity that were given MitoQ in the drinking water and then fed a high-fat diet experienced a marked decline in total body mass and fat mass compared to mice fed a normal-fat diet.[35] Mice given MitoQ and fed a high-fat diet also ate less food. Furthermore, MitoQ reduced fatty liver related oxidative damage.[35]

In another study by the same researchers, a dose of 500 μmol/L dose of MitoQ given to already obese mice caused the animals to drop too much weight and drink too little water so the researchers cut the dose in half.[36] In this study, MitoQ had modest anti-obesity benefits. Primarily, MitoQ resulted in a robust decline in plasma leptin, an important marker of fat mass.

Diabetes and Metabolic Syndrome

Mitochondrial dysfunction is associated with the development or progression of metabolic syndrome, a cluster of risk factors for cardiovascular disease including high blood pressure, abdominal obesity, high blood sugar, and elevated low high-density lipoprotein cholesterol (HDL-C) levels. Researchers studied the effects of MitoQ on muscle lipid profile alterations and mitochondrial function in rats fed a diet prone to develop obesity.[37] The study authors divided 24 young male rats to receive a high-fat diet, a high-fat diet with MitoQ, or a placebo. The high-fat diet triggered the development of obesity, hepatic enlargement, and glucose intolerance, features of the metabolic syndrome. MitoQ supplementation suppressed the increase in body weight and decreased the increase in fat tissue and liver weights in the animals fed a high-fat diet. It also partially reversed glucose intolerance. The high-fat diet caused increased triglyceride accumulation and important alterations in the muscle phospholipid classes and in the fatty acid composition of total muscle lipid. A decrease in mitochondrial respiration accompanied these changes. However, MitoQ supplementation stopped the lipid alterations and restored mitochondrial respiration.

In another study assessing the effects of MitoQ on leukocytes from patients with type 2 diabetes mellitus, MitoQ demonstrated anti-inflammatory and antioxidant abilities, including inhibiting ROS generation, decreasing interactions between leukocytes and the lining of blood vessels known as the endothelium, and inhibiting the inflammatory marker tumor necrosis factor-alpha (TNFα).[38]

Anti-Aging Effects

Oxidative stress is implicated in much of the cellular and tissue damage that occurs during aging. MitoQ may therefore be a useful agent in middle-aged and elderly individuals. Its anti-aging application was demonstrated in a recent study where MitoQ resulted in a pronounced inhibition of telomere shortening in human fibroblasts.[39] Telomeres are the protective caps on the ends of chromosomes and a reduction in telomere length is associated with aging. MitoQ treatment also was associated with an average 40% increase in the replicative lifespan of the cells.[39]

MitoQ has also been studied for its effects on age-related endothelial dysfunction. Mitochondrial dysfunction is a major source of the oxidative stress implicated in arterial endothelial dysfunction. Endothelium-dependent dilation of arteries is reduced in old mice.[40] However, MitoQ supplementation completely restored endothelium-dependent dilation in older mice by improving nitric oxide bioavailability.[40] MitoQ-induced improvements in endothelial function were related to normalization of age-associated oxidative stress and increases in indicators of vascular mitochondrial health, such as antioxidant status. During aging there is an increase in the susceptibility of arterial endothelium to acute mitochondrial damage. MitoQ reversed this susceptibility.[40]

Cardiovascular

Oxidative stress originates when there is an imbalance between the production of ROS and antioxidant synthesis. Oxidative stress is an important factor in the development of cardiovascular diseases such as atherosclerosis, ischemic heart disease, heart failure, stroke, and hypertension.[41] Mitochondrial dysfunction can lead to the excessive production of ROS and is often involved in the origin of cardiovascular disease.[41,42]

MitoQ is therefore a logical choice to support cardiovascular health. In animal models of heart transplantation and heart attacks, MitoQ has been found to protect against ischemia-reperfusion damage, injury that occurs when oxygen is introduced back into oxygen-starved arteries.[43,44]

In stroke-prone spontaneously hypertensive rats, a combination of MitoQ and low-dose losartan (a blood pressure medication) resulted in synergistic benefit.[45] The combination markedly reduced development of hypertension and left ventricular hypertrophy. Furthermore, in cell culture, MitoQ directly suppressed hypertrophy of heart muscle cells (cardiomyocytes) from rats.[45]

Another beneficial application for MitoQ may be for individuals taking cholesterol-lowering drugs.[46] Cholesterol and other isoprenoids produced via the same pathway are required by CoQ10 to attach it to the inner membrane of the mitochondria.[46] Therefore, cholesterol-lowering drugs reduce CoQ10's availability to the mitochondria, and MitoQ could replenish the mitochondria's supply of CoQ10 in people on these medications.[46]

The utility of MitoQ for cardiovascular protection was recently investigated

in humans, in a study of older adults (males, 60-79) at Colorado University.[47] Alongside other benefits the results showed those taking MitoQ for six weeks experienced an average of 48% improvement in arterial function.

Conclusion

CoQ10 is an antioxidant that is well-known for the important part it plays in mitochondrial function. However, supplemental CoQ10 does not easily penetrate the mitochondrial membrane. A new form of this nutrient known as MitoQ combines the ubiquinol form of CoQ10 with the lipophilic triphenylphosphonium cation, significantly increasing its ability to enter into the mitochondria. In human trials, this mitochondria-targeted nutrient has been shown to support liver health in patients with HCV, improve arterial function in older adults, and reduce pain and improve memory in individuals with fibromyalgia. Additional human trials are being conducted or are in the planning stage. Animal studies also suggest MitoQ may enhance brain health, support a healthy weight, suppress components of metabolic syndrome, have anti-aging effects, and be involved in cardiovascular health.

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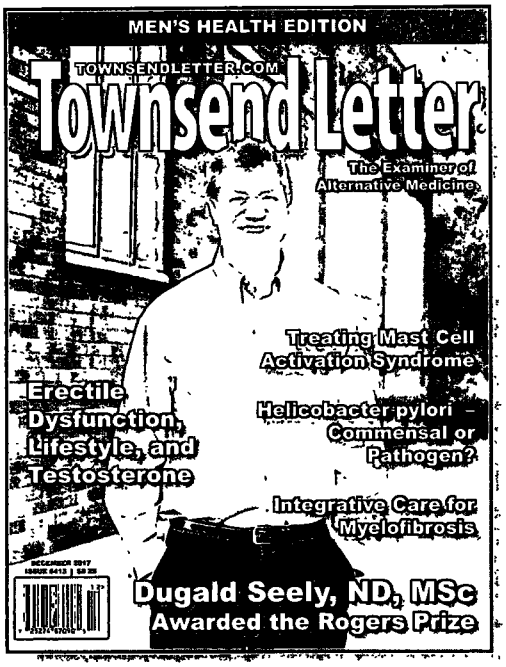
Dr. Chris D. Meletis is an educator, international author, and lecturer. His personal mission is "Changing America's Health One Person at a Time." He believes that when people become educated about their bodies, that is the moment when true change and wellness begins. Dr. Meletis served as dean of naturopathic medicine and chief medical officer for 7 years at National College of Natural Medicine (NCNM) and was awarded the 2003 Physician of the Year award by the American Association of Naturopathic Physicians.
www.DrMeletis.com

Dr. Suzanne Bennett is an internationally recognized natural and integrative medicine expert with over 27 years of clinical experience in the fields of allergies, clinical nutrition, methylgenetics, and anti-aging medicine. She's the founder of the Wellness for Life Center in Santa Monica, California, and author of *Mighty Mito* and *The 7 Day Allergy Makeover*.
dr@drsusanne.com

Kimberly Wilkes is a freelance writer specializing in health, science, nutrition, and complementary medicine. She has written more than 300 articles covering a variety of topics from the dangers of homocysteine to sugar's damaging effects on the heart. She is the editor of *Complementary Prescriptions Journal* and enjoys scouring the medical literature to find the latest health-related science.



On the cover

Dugald Seely and the Rogers Award

Small Country-Big Prize: What's the Story?

by Jacob Schor, ND, FABNO

On the evening of September 14th, 2017, out dear friend and colleague Dugald Seely, wearing a tuxedo with a black tie, was awarded the Rogers Prize at an elegant banquet in Vancouver, British Columbia.

There are so many aspects to that single sentence that are amazing that I find myself sitting at my keyboard unable to type further. Attempting to describe this singular event has blown my brain's circuits, so to speak, making it difficult to even start.

It is so rare for the right person to get chosen for any big prize that this in itself is a starting point. I so often find myself cheering for the runner-up, the honorable mention, the poor sucker who almost won, the loser as it were, that being on the winner's side is something of a shock. The one thing that makes sense about any of this is that Dugald Seely is unquestionably a true leader, advancing integrative health care in Canada, unarguably deserving of this prize. That part is indisputable.

But let me break this stupefaction down further so our readers comprehend why I am incredulous. Let us start with the prize.

Since 2007 the Rogers Prize has been awarded every second year to a practitioner who has contributed to complementary and alternative medicine in Canada. Catch that last word, Canada.

This prize is only given to people who live in that country to the north of us. It's certainly a big country, but not many people live up there. Back in 2015 when their total population topped 35 million, Canadians got excited and celebrated. Keep in mind that California alone has as many people. Imagine spreading out all the people in California from Newfoundland to Vancouver Island and as far north as Hudson Bay. People are sparse and far between up there. The US has almost ten times Canada's population. Yet Canada has the Rogers Prize, well properly known as the "Dr. Rogers Prize for Excellence in Complementary and Alternative Medicine," and we don't.

The Rogers Prize isn't just some somber plaque to hang on your wall. It is a cash prize: a two hundred-and-fifty-thousand-dollar cash prize. Granted that these are Canadian dollars awarded, but California has nothing to compete with this. The entire US of A has nothing to compare.

Our Canadian friends know that Lotte and John Hecht of Vancouver fund the Rogers award; and they all have let me know that these generous benefactors, while not anonymous, don't want publicity, so they mention this quietly.

The US did have the Bravewell Award of $100,000 for a few years that was last presented in 2013 to Dr. Oz (see Bravewell.org), and though the prize was for leadership in integrative medicine, only MDs ever received the prize. A country one tenth our size sees fit to present an award that is twice the amount of the Bravewell Award and then gives it to a naturopathic doctor. Actually plural, naturopathic doctors: Don Warren, ND, received a "Groundbreaker Award" this year as well. This says something about the relative appreciation of integrative healthcare and naturopathic physicians in our two countries, but exactly what does it say?

"The Dr. Rogers Prize recognizes" according to their website, "those who embody the same level of vision, leadership, and integrity as that of the late Dr. Roger Hayward Rogers. Among the first physicians to provide non-traditional therapies for cancer patients, Dr. Rogers was appointed to the Order of British Columbia in 2001, in recognition of his ground-breaking work."

Ponder that for a moment. Dr. Roger Rogers. In our country we would ridicule someone whose first and last names were nearly identical. In Canada, Roger Rogers is appointed to the Order of BC. In the US, doctors who encouraged the use of alternative medicine to treat cancer in decades past lost their licenses and were forced to practice in Mexico.

I asked Joe Pizzorno, ND, who served as one of the award jurors that chose Seely, about the differences between Canada and the US. He didn't think actual clinical practice differs appreciably, just that they, the Canadians, were ahead of us when it comes to integration and cooperation: "I don't see any difference between integrative medicine in the US and Canada. However, a case could be made that historically, Canadian integrative medicine organizationally started before the US. I think that Orthomolecular Medicine was first."

We might point out that Health Canada adopted the Determinants of Health concepts in the early 1970s.[1] To put this into context, recall that *JAMA* had accepted tobacco advertisements in its journal up until 1954, and the American Medical Association didn't call for a ban on cigarette advertising until 1985.[2] Tobacco advertising has been illegal in Canada since 1988. We've been playing catch-up with Canada when it comes to public health for quite a while.

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The Family: A Seely of Doctors

by Jacob Schor, ND, FABNO

There are specific names for collectives of various types of animals. You have seen the lists: a "pride" of lions, a "shrewdness" of apes, a "parliament" of owls, a "cauldron" of bats, a "troop" of monkeys, and so on. Reading about Dugald Seely's family background, I want to propose a new collective grouping, a "Seely" of doctors. They are all doctors, generations of doctors. Seely's great-grandfather Dr. Dugald Christie, established the first Western-style medical clinic, then hospital, and finally medical school in Shenyang, China, in the late 1800s. His grandfather Dr. Ronald Christie worked with Fleming to develop penicillin and was Dean of Medicine at McGill University. There's still an award, the Christie Award, named after Ronald, which is presented by the Canadian Association of Professors of Medicine to an outstanding member each year. Our Dugald's grandmother Phoebe Seely was one of the founders of Meals on Wheels. Dugald's late father, Dr. John F. Seely, was an internationally recognized clinician; he passed away from cancer in 2009. John Seely was Dean of the Faculty of Medicine at the University of Ottawa and developed the palliative care program for The Ottawa Hospital.

Dugald's mother, Dr. Janet Christie-Seely, is a family therapist, teaches family medicine at the University of Ottawa, and practices family therapy. Janet focuses on "systems theory" in her practice, looking at family interactions or the family as a whole and how these correlate with illness.

"My father was greatly supportive of the vision for the OICC and joined the board of governors of the Canadian College of Naturopathic Medicine before his diagnosis. He fully believed in and exemplified whole-person, patient-centered care. A medical doctor like many in my family, my father was wholly supportive of integrative medicine and an approach to care that benefits the patient the most." – Dr. Dugald Seely, ND

Dugald Seely is one of four siblings that all practice medicine. His older sister Jean is head of breast imaging at the Ottawa Hospital. Dugald's brother, Dr. Andrew Seely, is an intensivist and thoracic surgeon at the Ottawa Hospital. This is how *Ottawa Life Magazine* described Andrew's specialization: "Andrew is an international leader in the bedside application of complexity science using mathematical analysis of patterns of variation of vital signs."[3] I guess I can be forgiven when I don't always follow what Dugald is talking about. Look where he comes from!

Dugald's sister Allison is a veterinarian who has specialized in providing chiropractic care to animals of all sizes, from cats to horses. Dugald is the youngest of the family and continues a long tradition of clinical practice that is dedicated to supporting patients. The fact that he has embraced naturopathic medicine has not dimmed an appreciation of conventional medicine or rigorous science. Living with his family, he has had to learn the value of integrating alternative medical practices with conventional medicine. No, that isn't right. Heidi Vincent who works with both OICC and ONCANP corrects me: "He didn't 'have' to learn to come around to integrative medicine...he had an openness of bringing the two modes of care together from the beginning, which he instinctively learned, given that he was part of a conventional medical care family."

Keeping with the familial theme, Sarah Young, Dugald's wife, has also been a major contributor in the creation of the Ottawa Integrative Cancer Centre. Following a two-year feasibility study they conducted after moving to Ottawa in 2009, the OICC was opened in the fall of 2011. Currently the center sees over 700 patient visits monthly, caring for nearly 500 unique new patients and their families annually.

Dugald Seely has inherited a family model of dedicating one's life to closely caring for individual people while at the same time stepping back far enough that he can examine the practice of medicine in a larger perspective so as to ponder how to advance the field as a whole. See why I'm only half joking about this collective term; it's easy to say that Dugald comes from a Seely of doctors. Or perhaps we could turn it the other way around and instead say, an "integration" of Seelys in order to describe a family reunion.

Dugald Seely and the Rogers Award

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But back to Vancouver, who would have ever imagined Dr. Seely dressed up in a black tie and tuxedo? This is amazing. Dugald has always been and always will be the guy with sleeves rolled up, the guy who is so hard at work that he doesn't dress up. Suits don't fit him. Looking at his photo holding the prize, I can't help but smile in disbelief.

The online bios of Seely call him a "clinician and researcher, the author of numerous scientific reviews on complementary medicine...." Talk about understatements. Plug "Seely, Dugald" into a PubMed.gov search and it spits back 72 citations. Does he have competitors within our profession? Well yes, Heather Greenlee has 87 citations, but she's a full time academic at Columbia University. Dugald is, as his bio says, a clinician who sees patients for a living.

Reading through his published work, you want to describe it all as 'research with a purpose.' Lise Alschuler, ND, is the one who pointed this out to me:

> One important attribute of Dr. Seely is his consistent and long-term clinical practice. The reason that his research efforts are so clinically impactful is because he approaches the research as a clinician first and as a researcher second. All of his research answers clinical queries and has immediate translational value to the practice of oncology. The importance of this cannot be overstated. In times when new research is completed at an almost overwhelming rate, research that is informed by clinical needs becomes the fulcrum of change and practice innovation.

If you doubt Dr. Alschuler, read through that Pubmed list and notice the topics Seely's covered. His clinical trials have examined naturopathic medicine and cardiovascular disease (2013) and whether it is cost effective, whether naturopathic medicine is effective for chronic low back pain (2007), for anxiety (2009), for tendinitis in postal workers (2009 and 2013) and whether vitamin supplements can prevent HIV transmission from mother to child (2005). He has led teams of academic reviewers who have performed systematic reviews and evaluated among other things, black cohosh and breast cancer, selenium and lung cancer, Vitamin D safety in cancer patients, green tea and lung cancer, flax and breast cancer, Vitamin A and lung cancer, melatonin and cancer, ionic footbaths, green tea and breast cancer recurrence, soy and red clover in breast cancer, fish oil in prostate cancer, both in vitro and in vivo and analysis of Essiac, metronomic dosing of chemo in pediatric cancer, EDTA and cardiovascular disease (CVD), African herbs for HIV, ginseng use during pregnancy, cinnamon and diabetes, supplement interactions with chemotherapy in pediatric cancer, niacin for migraines, acupuncture for stroke, thermography for breast cancer screening, supplement interactions with CVD drugs, and black cohosh safety during pregnancy and lactation. He was also a key contributor to the guidelines for integrative therapy use during breast cancer treatment. This list isn't complete. I got tired of typing. Those of us who practice naturopathic oncology rely on Seely's work; to say it is invaluable in daily practice would be an understatement.

Dr. Seely is the founder and executive director of the Ottawa Integrative Cancer Centre (OICC), where he and his team of 26 are pioneering a contemporary cancer treatment model based on "scientifically grounded, evidence-informed complementary medicine." With the 2011 establishment of this first integrative cancer care and research center in Eastern Canada, Dr. Seely's team provides whole-person care to people living with cancer and addresses research gaps in cancer care.

Dr. Seely completed his MSc in cancer research at the University of Toronto and is a Fellow of the American Board of Naturopathic Oncology (FABNO). He is currently the vice-president of the Oncology Association of Naturopathic Physicians (ONCANP). As a clinician scientist, Dugald has been awarded competitive grant and trainee funding from

The Thoracic-POISE Study

by Jacob Schor, ND, FABNO

Dugald Seely, ND, and his brother Andrew Seely, MD, are the co-principal investigators in this first of its kind research trial to determine if naturopathic therapies can help thoracic cancer patients to improve long-term survival and adverse events associated with surgery. Lung, esophageal and gastric cancer patients are all included in the trial. Ottawa, home of the Seelys, is the primary site. The trial protocols have been developed from previously published work.

In a recently completed randomized clinical trial, another study co-led by the Seely brothers, 710 participants were enrolled in collaboration with the Canadian Association of Thoracic Surgeons in eight hospitals across Canada. This earlier study called AMPLCaRe, explores the effect of melatonin for lung cancer recurrence and survival results of which are expected to be ready and published within the next 6 to 12 months. According to *Ottawa Life Magazine*, "If trial results reflect what has been shown in other studies, there is real potential for reducing lung cancer recurrence after lung cancer resection, and thus improving quality and efficiency of care to the health care system through the use of this low cost non-patentable natural health product."[3] This study and the new TPOISE trial are compelling examples of the pioneering complementary cancer care research efforts led by Dugald.

CIHR, CBCRA, the SickKids Foundation, the Lotte and John Hecht Memorial Foundation, the Ottawa Regional Cancer Foundation, and the Gateway for Cancer Research.

While Dr. Seely has led numerous research projects over the years, his largest and most exciting project is the ongoing Thoracic-POISE study. Just three years ago, in October 2014, Seely announced the $3.85 million-dollar grant that is allowing him to study the addition of naturopathic medicine to conventional care for lung, gastric and esophageal cancers. This is the largest research grant for naturopathic medicine ever awarded. The full title is a mouthful: "Thoracic Peri-Operative Integrative Surgical Care Evaluation" (or Thoracic POISE). The project's goals are twofold. First, it is pioneering the naturopathic interventions to use before and after cancer surgery. Second, it will fund a randomized controlled trial to evaluate if the integrative care approach reduces adverse events and improves disease-free survival. A multi-center network of Canadian thoracic surgery centers, partnering with naturopathic doctors, will collaborate over an 11-year period in this 300-patient study. [NCT02845479]

Dugald has brought this same pattern of using research to inform clinical practice to the Oncology Association of Naturopathic Physicians where he chairs the research committee. He has been instrumental in pioneering an

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KNOWoncology.org

by Heather Wright, ND, FABNO

For the past several years, the Oncology Association of Naturopathic Physicians (ONCANP) has funded an initiative to assemble human level data on natural therapies in cancer care to help our members better access, understand, and refer to the evidence basis of our medicine.

The goal was to provide members ready access to curated data to allow for meaningful discussions with patients and other providers. This project is led by KNOW project research directors Jen Green, ND, FABNO, Heather Wright, ND, FABNO, and Dugald Seely, ND, FABNO, and is supported by research assistants Anne Thiel, ND, Julia Dean, ND, and Sarah Soles, ND, in addition to others as well as volunteers.

Becky Skidmore, BA, MLS, a research librarian, helped design both the PubMed CAM search filter as well as an expanded and more detailed CAM search filter with input from naturopathic doctors in oncology specifically for KNOW to help find increased numbers of relevant studies vs. the standard PubMed search.

The initial KNOW literature search looked at clinical trials using natural therapies related to 'breast cancer' in PubMed and Embase (the European equivalent) and yielded over 54,000 citations. Reviewers screened these articles using a program called Abstrakr, selecting ones that met inclusion criteria and excluding others. Selected articles are uploaded to the website using a reference manager software called Mendeley. Full text articles are pulled for these studies and reviewed by a team of research assistants who summarize and tag them.

Thus, for breast cancer, the original 54,061 papers were winnowed down to just 451 papers. For neuropathy, the 1500 initial papers were reduced to 40 and for curcumin, the initial 1200 were reduced to 18. This process occurs to select papers that are clinically meaningful and that meet criteria specific to integrative oncology.

After those four initial topics, (breast, neuropathy, curcumin and thanks to Dugald Seely's interests, lung cancer) were included in a beta version of KNOW, the search methodology was shifted to make the process more efficient and improvements continue. KNOW was presented at the conference for the Society of Integrative Oncology in Miami in 2016, and at the Oncology Association of Naturopathic Physicians conference in 2017, and supplied both oral and poster presentations to each. To date, KNOW holds about 750 human clinical trial summaries, and these are searchable in the database. KNOW website also has an 'unsummarized' section that contains articles that are waiting to be summarized and tagged.

The KNOW project team plans to continue to search PubMed and Embase each year using their specialized filters to get relevant articles on integrative oncology human studies for that year. Currently, KNOW searches include data from 2010-2016. Summarizing articles is a rigorous process. The KNOW team of five research assistants working five hours a week completed about 275 summaries over the summer.

KNOW also contains files of support literature, which includes a range of handouts, protocols, and other work authored by naturopathic doctors. Submissions are always welcome. These allow the expert group of physicians to share with those starting out, and this dialogue is supportive to raising the bar of the profession.

At this point in time, use of KNOW is limited to OnCANP members who can cut and paste citations or whole summary charts into emails or word documents for best communication and collaboration on treatment plans or with providers. In the future, KNOW project hopes to be able to license copies to other organizations so that their members will have access. KNOW also looks to develop collaborations that will add new data to the site and support in-kind work. One goal in the future is to cover data on topics that have been excluded from KNOW to keep the numbers manageable. Topics such as mind-body therapies and acupuncture are yet to be added, and the KNOW project looks to forge partnerships with other research groups to help add these segments of research to widen the holdings that are of interest to clinicians in cancer care. The KNOW project's newly formed advisory board, made of leaders in integrative oncology, is helping the project improve and grow.

online database of clinical trials, which our membership uses to inform clinical practice. Known by the acronym KNOW for "Knowledge in Naturopathic Oncology Website," this is the largest and most expensive project ONCANP has undertaken. Let me confess here that it has been Dr. Seely's steadfast lobbying of ONCANP's board of directors, including myself, that has kept KNOW alive and kept me usually voting in favor of the project despite my fears that it could turn into a perpetual and bottomless financial sink hole. When this KNOW site is fully operational and everyone is praising ONCANP's foresight, much credit should go to Dr. Seely for his prescience.

We are banking on this prescience thing. It was from David Schleich, PhD, that I first heard the term prescience to describe Dr. Seely:

> Dugald Seely knows that the Canadian naturopathic profession has had considerable savvy for several decades about the patient-driven need for wide access to natural medicine modalities and protocols. His tireless work enhances the profession's responsibility to blend the best evidence with the powerful practice traditions of CAM long in place in Canada.
>
> Dugald Seely is a remarkably prescient and skilled research professional who knows what we have to get done now. The Roger's Prize is a special, strong statement about his gifts and his tenacity. (2017)

Aside from responsibilities already mentioned, Dr. Seely serves as the director of research and clinical epidemiology at the Canadian College of Naturopathic Medicine and is an affiliate investigator for the Ottawa Hospital Research Institute. Dr. Seely is also a section editor for integrative oncology in the journal *Current Oncology* and a past board member for the Society of Integrative Oncology (SIO). Dr. Seely was also appointed to Health Canada's Expert Advisory Panel for the Vigilance of Health Products on which he served three years.

Iva Lloyd pointed out to me via email that, "Under Dugald's leadership, as director of naturopathic research at the CCCM for over ten years, he has created the largest naturopathic research department in North America and one that continues to be recognized on the international research stage." In fact, no end of prominent people in the naturopathic profession have pointed out to me that Dr. Seely seems to be everywhere in Canada and has no shortage of associations with various entities that have long names that are capitalized and often turned into acronyms. We may have to add a glossary at the end of this article

What is hard to convey by listing all these hats Dr. Seely wears during his workday and by listing his steady published study output is that he is a nice guy. Again, Dr. Alschuler:

> With a 25-page curriculum vitae, one might suppose Dr. Seely to be either entirely reclusive or a braggart. However, nothing could be farther from the truth. Despite his herculean work ethic and staggering accomplishments, Dr. Seely is one of the most kind, respectful, engaging and delightful people that I know. He builds consensus, cares about the ideas of others, is passionate about the future and, above all, is fundamentally dedicated to the betterment of the human community.....
>
> I am so thrilled for Dugald – literally smiling ear to ear! Dr. Seely has led the charge for the validation of the practice of naturopathic oncology in Canada and North America.

Of course, there is an elephant trampling around in the background, one of those big obvious things that I have so far failed to mention. There is a fundamental difference in Canadian healthcare compared to healthcare in the US that cannot help but impact complementary and alternative practice in their country. Basic healthcare is afforded to every Canadian resident. Healthcare is considered a basic right of citizenship. Try to explain that to a US citizen. It is hard for us to comprehend. Try to explain monthly insurance premiums, co-pays and the need to meet a deductible before care is reimbursed to a Canadian; this is impossible for them to comprehend. If they nod their heads yes, pretending to understand, take it a step further: explain the increasing frequency of elective procedures late in the year after people have met insurance deductibles. Most of us speak English, but the fundamental realities that separate our countries couldn't be wider. So yes, integrative healthcare is more evolved and better appreciated in Canada. The Rogers Prize is amazing but so is Health Canada; healthcare itself is a basic human right in Canada. Here in the US, this simple idea is still open for debate.

So, congratulations, Dr. Seely, and well done, Canada, for having the prescience to appreciate him.

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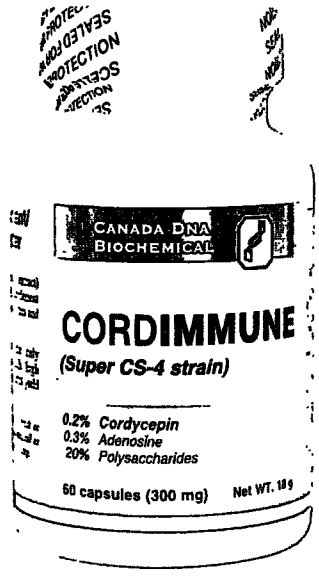

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A Crash Course in Erections and Testosterone

by Jade Teta, ND

As a naturopath, who spends a lot of time in the gym and fitness realm, I am often asked health-related questions. Reflecting on some of these questions, I realized there is an underlying theme for many of the men who seek me out.

Recently, I had a question asked by an acquaintance who made it clear, he was uncomfortable asking. The short of it is, this guy is a lifter. He is fairly healthy, beyond healthy, compared to the average Westerner. He does mostly all the right things. Sure, he drinks a little and stresses a lot. But who doesn't, right?

He told me he has been fatigued, lacking motivation and drive for almost a year. He has slowly been gaining weight around the middle. Not enough that anyone else would notice, but he sees it. He has also starting to get soft around the chest. This is fairly common in men in their mid-thirties to forties, but not so common in a lifter. None of this bothered him too much, and then he told me about his erections. They are incomplete, unsustainable, and sometimes don't come at all. This was the part that is obviously the most upsetting because his tone became desperate.

I hear all of this, and I have two questions for him. First, are you on any type of anabolic steroid, or did you just get off of them? I ask this because he is a weight lifter, and steroid use is so common. A well-known symptom of anabolics is, when you come off of them, the body has difficulty picking back up its own production of testosterone. The second question is when did you last have your testosterone levels checked? He answers "no" to the first question and "never" to the second question. This tells me I am going to need to give him a crash course in both erections and testosterone.

A Crash Course in Erections

Obviously, his major concern is the erections, but there is much more going on. Let me walk you through what I am thinking, as a naturopathic physician.

The male erection is a closely orchestrated event between the nervous system and blood flow into and out of the penis.

The brain registers a "sexually relevant" cue. This could be any number of things, and the stimulus response depends on the man. It may be cuddling up with his partner, seeing his partner walking across the room naked, maybe visual pictures or porn, while others may need direct penile stimulation. The point? The brain is where erections are made and they are often context dependent.

Assuming the brain is adequately sensitized to a sexual stimulus, nerve impulses are sent to the penis. This triggers a host of biochemical events that involve chemicals like nitric oxide (NO) being released, which then trigger cellular cyclic GMP (cGMP), which opens the blood vessels in the penis allowing more blood to flow in.

The penis is a pretty remarkable piece of physiological machinery. While blood flow is increased going in, a spongy layer of the penis, rich with capillaries, becomes engorged causing pressure to build up. This hydrostatic pressure causes the penis to inflate. This is all also contingent on a separate set of blood vessels that drain the penis. These vessels start to constrict under the increasing pressure and other biochemical events. The coordinated action of the incoming blood vessels, and the building pressure is what allows blood to rush in and stay in, creating an erection.

Where does testosterone get in on the action and contribute to this entire process? We will get to that in a second. First, I want to teach you a framework that will help you triage your own erection issues (or that of your partner). When you think of testosterone, libido, and erections, it is helpful to have a framework. The framework I use is the three Bs: brain, biochemistry, and blood flow.

The Brain

The sexual brain can be thought of as containing sexual stimulators and sexual repressors. Emily Nagowski, PhD, author of *Come as You Are: The Surprising New Science that Will Transform Your Sex Life*, calls these "accelerators and brakes." In order for sexual desire to occur and sexual arousal to engage, the accelerators need to be turned up while the brakes are turned down.

It kind of works like this: You are sitting on the couch working frantically to get a proposal done for work. You are stressed. Your partner sits down next to you, and starts rubbing on you. You register a "sexually relevant stimulus" in your brain. This hits the accelerators. But, before you can really get aroused, the brain checks in on the context. It says, "This is nice, but I have to get this

stuff done." The stress you are under puts the brakes on.

The degree to which the stimulus can amplify the accelerators, and the stress holds on the brakes, will determine the quality of the erection response.

Many people get this all wrong. The brain is at work here, and it is not just an automatic stimulus response apparatus. There is much more going on. By the way, men, women have far more sensitive brakes compared to men. This is why foreplay and context are so much more important to their sexual arousal, desire, and function. It is also the same reason alcohol, or a first date, may result in a weak erection or a complete lack of erection for a guy, despite his strong desire. Every man, and likely most women, has experienced this phenomenon.

The brain is critical. Relaxation and adequate nerve stimulus to the penis is required. Women, it has nothing to do with you. And, guys, it is completely normal to occur on occasion.

To understand this brain effect better, think "**P**oint and **S**hoot." The two branches of the nervous system are **P**, parasympathetic, and **S**, sympathetic. Parasympathetic is relaxing, and sympathetic is stimulating. The balance of the P and S is critical. To get an erection, you need adequate P, or parasympathetic outflow. Think P, for Point, to remember this. To ejaculate requires adequate sympathetic outflow. Think S, for Shoot, to remember this.

A man who ejaculates too quickly and/or has weak erections may be dealing with poor parasympathetic (relaxing) outflow. This may be due to being overworked, overwhelmed, alcohol, stress, mood, medications, or any condition that disrupts nerve signaling – the most common being diabetes.

A man who is unable to ejaculate or takes longer to ejaculate may be suffering from the opposite: Poor sympathetic outflow. This, too, can be caused by stress, overwork, overwhelm, mood medications, and diabetes. This also may be a sign of the use of Viagra or another PDE5 inhibitor. For younger men, who are not overweight, this is almost always a result of some type of stress effect or medication since most are not dealing with diabetes. My friend was an example. We could assume the brain piece of this was fine.

Another brain concern has to do with the command and control center of the metabolism. The hypothalamus is an area of the brain that receives signals from other hormones and coordinates other hormone-producing organs in the body. The hypothalamus registers all the signals from the environment (sight, sound, temperature, etc.) and signals from inside the body (exogenous hormones) then adjusts the metabolism as needed, much like a thermostat.

As it pertains to the testes, the hypothalamus releases gonadotropin releasing hormone (GnRH), which binds in the pituitary and triggers the release of luteinizing hormone (LH). LH then travels to the testicles, aiding sperm production (mostly the job of FSH), and turning up testosterone production.

If this hypothalamus-pituitary-gonad communication link is compromised, it can dramatically impact testicular function and testosterone. Testosterone inhibits feedback at the hypothalamus and can also be converted to estrogen via the enzyme aromatase. That estrogen plays a role in feedback to the pituitary, which is why SERMs (selective estrogen receptor modulators) like tamoxifen, are sometimes used in men.

The estrogen effect may come to be a major player here. We do not yet have proof, but many natural medicine practitioners, like myself, believe the sharp rise of low testosterone in young men may be connected with the estrogen saturation in our environment. Estrogen-like compounds are everywhere now. They are in our water, leach out of plastics, sprayed on our food as pesticides, and accumulate in the fat and milk of the animals we eat.

So, when we think "brain," we also want to be thinking hypothalamus. The other interesting thing here is that the hypothalamus and pituitary are also responsible for thyroid and adrenal function. These are so critical to metabolic function; they are referred to as HP-axis (hypothalamus-pituitary-thyroid axis (HPT), hypothalamus-pituitary-adrenal axis (HPA), and hypothalamus-pituitary-gonadal axis (HPG, i.e. testicles and ovaries)). This will become important later.

This is why some therapies, like human chorionic gonadotropin (HCG), can be effective in multiple ways for men. It is also why low libido and low testosterone issues, coming from the brain, usually result in fatigue, sleep disruption, mood issues, weight gain, cold intolerance, etc. When the hypothalamus "takes a hit," it negatively impacts multiple downstream processes in the thyroid, adrenals, and gonads.

The Biochemistry

Given my friend is younger and fit, I am thinking his issue is biochemical, not brain or blood flow related. I have already covered some of the biochemistry of erection, but there is a ton more. Let's just stick with some of the more relevant material.

I already explained how the nerve signals transfer into biochemical signals, including signaling molecule cGMP and NO (nitric oxide). Let's cover this in a little more detail, as this is probably how testosterone gets involved in regulation of erection. When the brain sends nerve signals to the penis, NO is released and signals cGMP. This, then, dilates blood vessels and sets the erection cascade in motion with increased blood flow in and decreased blood flow out.

Cyclic guanosine monophosphate (cGMP) is broken down by an enzyme called phosphodiesterase 5 (PDE5). Since PDE5 degrades cGMP activity, if this enzyme is overactive, blood flow into the penis is slowed, and erection is either absent or incomplete.

This is how the erectile drugs Viagra, Cialis, Levitra, and others work. They each act as inhibitors to PDE5, prolonging action of cGMP activity, and therefore, allowing harder, longer lasting erections. Depending on the strength, their effects are short acting like Viagra (takes 30 min to kick-in and lasts 2-4 hours), or long acting like Cialis (takes a few hours to kick-in and lasts 18-36 hours). This may also be where low testosterone comes in.[1] Testosterone treatment increases NO activity and

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may stimulate healthy promotion of erectile tissue. Testosterone may also play a role in PDE5 inhibition because adequate testosterone levels are required for these drugs to work.

The brain is also impacted by testosterone. All the mechanisms as to how testosterone promotes libido and sexual function are not completely understood, but one of the hallmarks of any hormone is its ability to impact many enzymes and other hormone receptors involved in multiple areas.

Testosterone is likely acting as a priming apparatus for the male sexual brain and penile function. Without this primer, the entire cascade is disrupted.

Blood Flow

Ultimately, erectile function is really about a blood flow problem. If nervous system function is good and testosterone levels are adequate but blood flow is compromised, then erections are compromised.

For younger guys who are fit and not overweight, blood flow is likely not the primary issue. However, it will always be involved, which is why erection drugs work.

Erection issues in older men, overweight men, and those with metabolic syndrome or diabetes, however, are almost always about blood vessel issues. High blood sugar, high blood pressure, and inflammatory mechanisms are highly damaging to the cells lining the blood vessels. These are the same cells that are functioning through NO and cGMP.

This is why lifestyle effects are so critical to men. Most men jump to testosterone and erection drugs, but studies show complete restoration of erections in men as old as eighty when lifestyle is corrected.[2]

Erection issues are early warning signs of cardiovascular disease. Fixing the issue at this stage requires a complete overhaul of diet and lifestyle, including weight loss, decreased sugar and carb intake, weight training, stress reduction, and more.

Unless you want to be reliant on erection drugs the rest of your life (which become less effective over time if you don't correct the underlying issue) and you don't want to die of a heart attack or stroke, then change your lifestyle: eat right and manage stress.

Taking testosterone therapy in the context of an unhealthy lifestyle won't produce the expected results.

Lifestyle, Testosterone, and Erections

For most men under the age of fifty, not overweight, and no high blood pressure, the issue is likely brain or biochemistry related and NOT blood flow related. This is exactly what I was suspecting with my friend. One of the first things you will see in men with low testosterone is a lack of morning erections. Testosterone is usually at play here, as this is often a first warning something is up and a great biofeedback tool to measure progress with therapies. If the morning erections come back, this is a good sign.

I realize most men will want to jump right to testosterone replacement therapy, but not so fast. The thing you need to understand about hormones is that they work in symphony. You can't simply throw testosterone into the mix and expect it to fix the issues. Hormones work in context. They are like people and behave differently depending on the environment they are in. Make sure the overall biochemistry is optimized through lifestyle if you want testosterone to work correctly.

In other words, the first step is to live a testosterone supportive lifestyle. The things that raise testosterone are the following:

- Adequate macronutrient intake – in other words, enough but not too much protein, fat, and carbohydrate.
- Adequate calorie intake – not too much and not too little.
- Adequate intake of micronutrients. The three most important for testosterone may be zinc, magnesium, and vitamin D. Being low in any of these will compromise testosterone levels. Adding these in, if you already have adequate amounts, will likely do nothing but correcting deficiencies will.
- Weight training and intense exercise. Lifting weights reliably stimulates testosterone. Intense exercise, that is high volume and heavy loads, is best.
- Enough, but not too much, exercise.
- Lots of walking, since this sensitizes the body to insulin and lowers the stress hormone cortisol – both of which, indirectly and negatively, impact testosterone.

Diet and Exercise

Since the hypothalamus is essentially a stress barometer, you do not want to train too hard, too often, or for too long. You also don't want to go to dietary extremes by cutting calories and/or carbs too low. Do enough, but not too much; otherwise you risk downstream, negative effects flowing from a dysfunctional hypothalamus, which is severely and negatively impacted by insulin resistance and excess cortisol.

Blood sugar management and insulin sensitivity are critical to testosterone. There is a hormone called SHBG (steroid hormone binding globulin) that binds **very** strongly to testosterone, effectively removing it from the usable pool of hormones. Insulin resistance and excess cortisol both elevate SHBG. The end result is a reduction in usable testosterone, even when you are making enough. Also, excess cortisol and insulin have many other negative effects that disrupt metabolic function.

There are two dietary regimes I find useful as "off the shelf" advice for testosterone management: the 40-30-30 dietary regime for heavy exercisers and athletes and the 30-40-30 regime for everyone else. These formulas dictate the carb-protein-fat macronutrient ratios that I start most men out with. If men are overweight, I suggest a calorie intake that can be calculated by multiplying your body weight times 10. For those training heavily, the body weight multiplied times 15 is a good starting point. So, to reiterate:

- Calorie intake equal to 10 times body weight and a 30-40-30 diet for overweight, less active men; and
- Calorie intake equal to 15 times body weight and 40-30-30 ratio for all men engaged in frequent, intense exercise.

All guys dealing with this issue should be walking daily (best insulin sensitizer and cortisol lowering behavior), and lifting weights at least three times per week (testosterone promoter).

Remember, it is a mistake to take these kinds of rules as gospel. Use these as a starting place only. Adjust based on three factors:

1. Are your hunger, energy, cravings and other hormonal feedback (i.e. libido and erection quality) improving?
2. Is your body composition achieving the V-Shape? (See http://www.metaboliceffect.com/me-shape-calculator/)
3. Are your blood labs (especially free testosterone, total testosterone and SHBG levels) improving?

If all the above is true, then you are on the right track.

Testing and Labs

Once you get the diet and exercise under control, you want to make sure you get baseline labs. The labs recommended are the following:

- Testosterone (total and free),
- SHBG (if this is high to start with, diet and stress will need to be priority),
- High sensitivity estrogen (to rule out high aromatase. Some men aromatize testosterone to estrogen),
- Hemoglobin A1C (rule out high blood sugar and diabetes),
- Fasting Insulin (rule out insulin resistance),
- DHEA Sulfate (if low, supplementing can restore erectile function in 80%), and
- Vitamin D.

These should be done in addition to the general screening of lipids, CBC, and chem panel a doctor will do. Zinc and magnesium are also worth noting here; but since so many people are deficient and their supplementation has little risk, taking the supplement, ZMA, is likely wise and precludes the need for testing.

Research on things like horny goat weed, Longjax, and ForsLean, as well as other herbs and compounds, have little research supporting their use; and I personally have seen them as essentially useless clinically.

You can have these labs done directly at www.directlabs.com/metaboliceffect and www.CHEKD.com/metaboliceffect, both of whom I recommend. CHEKD.com is a great resource to manage all your concerns, from testing to replacement.

Some supplements you may want to consider include the following:

- DHEA, if DHEA sulfate is low. In one study, 50 mg DHEA restored erectile function in upwards of 80% of males who were low.[3]
- Vitamin D. Low vitamin D has been shown to impact testosterone, and restoring Vitamin D to levels between 50-100 ng/ml may raise testosterone; and it may help erections.[4]
- Citrulline malate. This is an amino acid that is a NO precursor and can act as a weak Viagra, assuring NO is abundant; 1.5g/day improved erections in men within one month.[5]
- *Rhodiola rosea*. This one is controversial, but I have personally seen it be effective. There are also, supposedly, some old Russian studies showing its benefit. I was never able to find the actual article/book that outlines these studies, but the reference is *Rhodiola rosea is a valuable medicinal plant (Golden Root)* (Saratikov, et al. Tomsk, Russia: Tomsk State University Press; 1987). I have seen people reporting that rhodiola increased testosterone, libido, and erection quality. Given rhodiola's favorable effects on the hypothalamus, this makes sense. Although most of the people I have seen respond were doing other things too, I can't say for sure this is effective; but, if you were my good friend, I would encourage you to take it (200-400 mg a day). It may also help premature ejaculation (makes sense given it is an adaptogen balancing the parasympathetic and sympathetic nervous system).[6]

Hormonal Approaches to Raising Testosterone

Okay, we are finally here. What happens if, when you test your levels, they are low? And, what is considered low? Most standard references for testosterone ranges are the following:

- Total testosterone normal = 300-1200 ng/dl (Many practitioners will treat if levels are below 500, and you have symptoms.)
- Free testosterone = 5-21 ng/dl

My recommendation is that a free testosterone below 10 and a total testosterone below 500 with testosterone-related symptoms, especially loss of morning erection, should be managed with the lifestyle changes and supplements listed above.

If there is no change after three months of concerted effort, then, and only then, consider testosterone replacement therapy (TRT). Keep in mind at this point that there is a difference between **replacing** testosterone and **enhancing with** testosterone.

When you do TRT, you are restoring normal levels, *not* trying to exceed them. Replacing to normal levels is not only beneficial for symptoms but, likely, one of the healthier things you can do.

Enhancing with testosterone by going over 1200 ng/dl is not necessary and may cause some issues. Remember, what you want when restoring testosterone is to bring your levels back to optimal *and* help the hypothalamus-pituitary-gonadal axis become healthier. Raising testosterone to levels beyond physiological works against this goal.

If levels are low right out of the gate, you have two options: (1) HCG monotherapy (and/or Clomid) and (2) testosterone replacement. One I prefer over the other.

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HCG Monotherapy

Human chorionic gonadotropin (HCG) is an LH analog. Meaning, it is biochemically similar enough to the LH hormone that it interacts with the same receptors. This means it can be used to turn on the testicular machinery, sperm, and testosterone production.

There are stories about HCG increasing ejaculation volume (this is true), and increasing penis size (this is true too, but it may only be the case for those with hypogonadism or "micro-penis"). The internet chat boards certainly are not without their stories of slight enlargement with HCG in normal men.

In the two studies[7,8] I found on micro-penis, the gains were three-quarters of an inch in length and girth. Anyone who has normal penis size and has gained these effects with HCG, I am sure all of us men would be eager to hear.

HCG is a great option because, unlike testosterone, it may actually help the hypothalamus gonadal axis as opposed to suppressing it. It also seems to have less impact on estrogen, prostate mass, and cardiovascular parameters compared to the more traditional TRT, being equal or better than traditional TRT in raising testosterone.

I realize this information may contradict other information around the internet as it pertains to HCG, but this assessment is evidence based and taken from a well-done study on men aged 45-53 with low T.[9] The study compared HCG against transdermal test, and two different injectables.

In fact, many doctors give HCG along with their testosterone therapies to keep the hypothalamus working and the testicles from shrinking.[10]

Why would the testicles shrink, you wonder? Testosterone from an outside source turns off the hypothalamus/pituitary secretion of LH; and therefore, the testicles stop producing sperm and testosterone. This is why ejaculate volume and testicles can shrink in men taking testosterone. This, usually, is not a huge issue if the drug is not abused. HCG helps keep this from happening.

As an aside, steroids do not shrink the size of the glans penis (i.e. the shaft), just the testicles, and only if used in very high amounts for too long.

Using HCG alone is a reliable promoter of testosterone and may be the safer, more natural option to start with, in those with HPG issues. It also may be the best approach for those of you who have been on testosterone for a long period of time.

Based on the studies, there are a few approaches. If using TRT, then 250 IU of HCG taken as an intramuscular injection (IM) daily is the approach recommended. If you are using HCG alone, according to the study above where it was directly compared to TRT, the dose was 2000 IU per week.

Most doctors don't like giving such a high dose of HCG all at once for fear of excess estrogen production and desensitization of LH receptors. Although this study did not show that, it may be a consideration.

Keeping any daily dose to 500 IU or less seems wise, which means you would be injecting 500 IU one to four times per week (500 IU – 2000 IU) for HCG monotherapy.

Clomid is another option in this regard. Clomid works by blocking estrogen hormone feedback at the hypothalamus. This increases natural LH production, which then stimulates testosterone production.

The dose for Clomid, at 25 mg per day or 50 mg every other day, has been shown effective in restoration of the HPG axis in men and very safe as well. At least in one study, Clomid compared directly to TRT outperformed testosterone treatment with no side effects from long-term use (up to 40 months).[11]

For those with secondary testosterone deficiency coming from the hypothalamus-pituitary axis, which is usually the case for younger men (<50 years), HCG and Clomid MAY be superior to TRT. As an aside, the cost of Clomid is vastly cheaper compared to TRT.

Testosterone Replacement Therapy (TRT)

The first consideration to be aware of is that steroids do not equal testosterone. Many men I have worked with will assume that, if they are taking anabolic steroids, they are taking testosterone. This is not the case, and an important distinction.

Anabolic steroids can be testosterone or androgen derivatives. Drugs like Anavar, Trenbolone, Winstrol, Primobolan, etc. have anabolic and androgenic effects similar to testosterone, but they are not testosterone. This means they are NOT suitable for TRT. Such drugs are also frequently the culprit for erection issues and low testosterone, especially after stopping them.

These "non-testosterone steroids" will shut down the body's own production of testosterone, like any other steroid, but will not be able to replace testosterone's full effects in the body. These are best left to bodybuilding circles.

Another consideration is the creams, gels, and orals of the pharmaceutical world. You can't patent testosterone; so to make money off of the therapy, drug companies tinker around with different delivery systems. These approaches are far inferior to injectable testosterone, and I would not use them, unless you are completely averse to injections.

The main drugs to consider are testosterone cypionate, testosterone enanthate, and testosterone propionate. The different compounds bound to the testosterone determine its half-life and, therefore, the dosing frequency. Cypionate (50-100 mg) is usually dosed one to two times per week, as is enanthate (50-100 mg). Propionate dosage is every other day at 25-100 mg per day.

There are two others: testosterone suspension and Sustanon. Testosterone suspension is 100% testosterone, while the three above are testosterone bound to esters that increase the half-life of the drug and make for a slower absorption. Suspension is rarely used due to the need for daily dosing and the rapid spikes and falls that occur with its use. Sustanon, too, is rarely used in

medical circles, mostly because it is not as widely available. It is a mix of the different testosterones and is a great option if you can find it.

Everyone has a favorite. For my taste, I like propionate more than enanthate, and enanthate more than cypionate. For some reason, propionate causes me to hold less water and just gives me a "cleaner look" and more even effects. But this is very much an individual thing.

Other Considerations

Of course, the biochemical pathways involved with testosterone therapy should be considered. Testosterone can be converted to estrogen via the enzyme aromatase. The use of aromatase inhibitors is beneficial in this regard, which is why many people will use Arimidex (anastrozole) along with their TRT.

Testosterone can also be converted into DHT, which may contribute to some side effects, including hair loss and acne; although, DHT may be a major libido enhancer.[12] This occurs via the enzyme 5-alpha reductase, which is why finasteride is often used with TRT as well.

The herbal world is filled with great aromatase and 5-alpha reductase inhibitors, often having both actions in one herb. I have found the use of products containing nettles, saw palmetto, pygeum, chrysin, and DIM a reliable way to control these two biochemical pathways without pharmaceuticals. The supplement I use is Androgen Complex (Metabolic Effect). The dose is six capsules daily.

Final Considerations

The final things to know when it comes to TRT are regarding testing and retesting. With TRT, we want to make sure we are not elevating prostate cancer and cardiovascular disease risks or other complications. You may want to consider monitoring PSA. This is a test, becoming more and more controversial, but still, may be the best we have to assess prostate changes over time.

You will also want to make sure hemoglobin and hematocrit levels are not going up while on therapy. This can increase the risk for blood clots.

Finally, watch estrogen levels and the liver enzymes ALT and AST to make sure you are not over aromatizing, and the liver is handling the therapy respectively.

Always take a close look at the free (direct), and total testosterone levels.

If you are doing things correctly, you should see favorable changes in your blood labs on TRT. Cholesterol, triglycerides, blood sugar, and inflammatory markers usually fall.

Obviously, testosterone is a requirement for male health, and proper TRT should be improving energy, mood, libido, erections, and body composition while also making you healthier.

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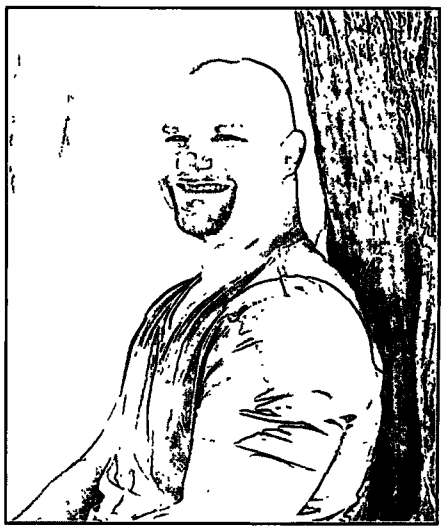
Dr. Jade Teta is an integrative physician, author and sought after expert in the realm of metabolism and self-development. He spent the last 25 years immersed in the study of strength and conditioning, hormonal metabolism and the psychology of change and success. He is the founder and creator of the international health and fitness company, Metabolic Effect, and the author of several books including the best sellers, *Metabolic Effect Diet* and *Metabolic Aftershock*. He has also contributed both, the exercise and sports nutrition chapters, to *The Textbook Of Natural Medicine*.



The Restoration Model

by Jean-Ronel Corbier, MD

The Restoration Model is based on the concept that a return to optimal health is possible. There must be some deviation from normal for illness to occur. This deviation can occur at any time, even very early on (e.g. before birth, or during the perinatal period, or during the first few years of life as with neurodevelopmental disorders). The deviation from normal can be caused by many factors that affect the victim through some form of trauma. Although the initial impact of the trauma can result in dysfunction, healing, and prevention of secondary problems are possible. It is always important to identify and treat the effects of the primary problem for restoration to occur. Traumatizing insults can be physical, emotional, psychogenic, spiritual, or a combination of these. Restoration necessitates fully addressing each of these areas.

The Restoration Model is based on the simple assumption that the body and brain have the intrinsic ability to heal themselves. A person can return to normal (optimal health) if the underlying problem(s) and their secondary affects are corrected. To affect this healing, though, we must use safe and effective tools. The Restoration Model is applicable to any illness or medical condition in adults or children. I will focus on one of the most complex, chronic, and multifaceted disorders and one that I am very familiar with, autism.

Details of the Restoration Model

I initially chose the term "Restoration" because it describes the intent of the model, which is re-establishment of health and wellness. I wish to discuss below the ingredients necessary for brain and body restoration. First, the model is based on the following premises:

- We all have self-healing bodies (including our brain that can rewire itself owing to its intrinsic neuroplastic properties). We are fully equipped with all the tools, processes, and the wisdom necessary to heal ourselves when we are sick.
- We are complex beings with a body, mind, and spirit. We have emotional and spiritual needs as well as more tangible bodily requirements. A disturbance in any of these areas can affect all the others.
- To remain healthy or return to health, we must follow a set of laws, regulations, and guidelines that promote wellness. There are no shortcuts.
- Violation of these health laws place us at great risk for all types of malfunction (spiritual, physical, behavioral, psychiatric or emotional).
- Total restoration is always possible although a great deal of time, effort and planning may be needed in complex and chronic cases.
- Because total restoration is possible, one should always maintain an optimistic and hopeful attitude. Patience is required. This attitude itself can contribute to health.

Psychosocial Factors and the Restoration Model

We live in such a fast-pace, high-expectation, individualistic society that it is very easy to get overwhelmed and stressed. There are more and more individuals developing anxiety and mood disorders. Even young children are having 'nervous breakdowns.' In keeping with these problems, I see a subset of children referred to me for neurological problems such as refractory seizures, gait abnormalities, weakness, or chronic headaches that sometimes turn out to have severe emotional disturbances that account for what appears to be a neurological problem. In other words, seizures, for instance, do not always have to be neurologic in origin. They can be psychogenic, the result of an emotional breakdown. An individual with non-epileptic seizures may not gain control of their 'refractory' or hard to control seizures with seizure drugs. The individual does not have an incurable case of epilepsy. Simply, the wrong form of treatment is being implemented for this patient. This scenario is not at all uncommon.

I had an adult patient whose seizures where so prolonged and unrelenting that the patient was about to be placed on a breathing machine (intubated) prior to being placed into a drug-induced coma to stop the seizures when it was discovered that the seizures were of psychogenic etiology. The patient revealed to the medical team that she was under a lot of stress and 'at the end of her rope.' Her stress was converted into an apparent seizure disorder. With appropriate counseling and support, this patient's seizures disappeared completely, without seizure medicines.

Many children with behavioral and academic difficulties of unclear etiology may have disorders that are largely

psychogenic in origin. Others may have low self-esteem. Many children get insufficient praise, which children need to thrive. Children need to believe in themselves. Their parents and teachers need to believe in them as well. And children need to know that their parents and teachers believe in them.

I took care of a child who had a lot of problems including a severe speech delay. This child's parents were told by other specialists that he would never talk because of the severity of his problems. He was almost five years old at that time. I saw him for several visits before he was lost to follow up. I saw him again after a couple of years and was pleasantly amazed to see that he was now speaking well and getting good grades in a mainstream classroom. I asked the family what made the difference in his language improvement. The answer was that he had moved to a new school where everyone believed in him and challenged him. He then blossomed!

Interestingly, the child also became healthier. Previously, he had many illnesses. A happy, secure, appreciated child is more likely to be healthy compared to a child who is under a lot of stress with a poor self-esteem. Studies in the field of psychoneuroimmunology suggest that mental attitude and emotional status can influence the competence of the immune system, which in turn can alter neurological function (Sheridan et al. 1994; Powell 2013). What this means is that a child with autism who is receiving all of the appropriate therapies (behavioral, educational, and biomedical including nutritional) and that does not make the type of progress expected may be experiencing psychological disturbances that are holding him back.

Biology and psychology are interrelated. Psychosocial factors can have a significant impact on neurological, cognitive, and behavioral functioning. The reverse is also true. Biological, nutritional, metabolic, and immunologic disturbances can result in neuropsychiatric disturbances. This is because the brain chemicals that control and regulate our mood and sense of well-being (such as serotonin, the 'happy hormone') require proper nutritional intake for their synthesis. All of the hormones, neurotransmitters and other chemicals are in some way dependent on nutrients such as amino acids, trace elements, vitamins and water for their proper synthesis and metabolism. These are indispensable for optimal health.

Psychosocial factors are not just important for the patient, but for the family as well since they are ipso facto enmeshed in the child's illness. The child's illness extends to the parents. The child's anxiety may also be the parent's anxiety. The child's stress is the parent's stress. The learned helplessness and pessimism of the child may also become that of the parents.' This may in turn further aggravate the child's level of dysfunction. Proper restoration requires that positive changes be experienced not only by the affected child, but also by the parents and everyone else involved in the child's life.

Spirituality and the Restoration Model

Medical science deserves an 'A' when it comes to advances in medical technology and in acute, crisis interventions, a 'B' when it comes to an understanding of psychosomatic interactions since doctors are finally beginning to understand that mental conditions such as stress and emotional disturbances have an impact on virtually every aspect of physical health. When it comes to spiritual matters, medical science gets an 'F.' In the Restoration Model, we expand the biopsychosocial construct as inspired by the work of Drs. George Engel (Engel 1977, 1980) and John Romano and add a spiritual component. We also consider the fact that biological derangements, whether congenital (present from birth) or acquired, can alter mental function and vice versa. Spiritual factors are also important.

In addition to making sure one's physical vital signs are normal and such parameters as blood pressure, blood count and blood sugar, it is important to pay attention to spiritual factors including love, kindness, compassion, faith, optimism, sense of purpose, resilience, determination, empathy, endurance, patience, altruism, and happiness. Though abstract, these factors can contribute to health and wellness. Likewise, spiritual practices, including meditation, can bring healing, affecting physical, biological, and spiritual factors as various studies have shown (Davidson 2003).

Therapeutic Mergers and New Solutions

There are many reports of individuals with autism who with early, aggressive, and appropriate treatment have improved so much that they no longer meet the criteria for the diagnosis of autism. The therapeutic interventions that produce these improvements are from varied fields (behavioral, educational, and biomedical). This suggests that different modalities can provide beneficial results that may be helpful although divergent in nature. In many other cases, however, there are children with autism who have tried

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many different therapies, spent time, resources, and energy but to no avail. These 'refractory' cases require a search for a missing link. A child with autism who has persistent symptoms despite the implementation of various therapies has either not found the right therapy or has a seemingly irreversible problem. I use the term "seemingly" because, as we shall see, 'irreversible,' 'refractory,' 'intractable,' and 'incurable' problems may have a solution.

First let me summarize the information that we have on the causes of autism and its clinical findings:

1. Autism (and many medical conditions in general) has a genetic component. There is not just one but several genes that are involved with autism.
2. Genetics alone, however, do not explain the full clinical picture. Non-genetic environmental causes play an important role, acting as triggers (Shaw 2017, Naviaux 2014).
3. Autism is a neurodevelopmental and neurobiological disorder that usually begins before the age of 3. The developing brain at that time is vulnerable to certain insults that cause dysregulation of neurons that subsequently affects the brain in specific areas (Corbier 2005).
4. Neuropathologic and radiographic studies show evidence that the brain is affected in several areas, including cerebellar, temporal, and frontal lobes. Various neural networks are involved (Wegiel et al 2010).
5. Immune abnormalities are present in many cases of autism, and inflammatory changes in neurons and neuroglia (supporting cells) have been noted (Chez 2010).
6. Children with autism have significant language, behavioral, and social issues that interfere with normal functioning. Their deficits can improve despite the presence of underlying brain dysfunction. This suggests that, despite the presence of subtle brain abnormalities in children with autism, these abnormalities may be one of many risk factors that contribute to the picture of autism. A search for the other triggers is important.

Changes in the structure of the brain in autism (and other conditions such as a stroke) does not mean that the brain cannot heal. We know that the body has self-healing properties, and the same applies to the brain, the command and control center of the body. Via the process of neuroplasticity, changes in the way the brain is wired can lead to brain restoration (Corbier 2017).

When it comes to making progress with a hard to treat condition such as autism, one should consider the following:

- Getting an early diagnosis.
- Starting treatment as soon as possible.
- Finding the right (set of) treatment(s).
- Being compliant with a given treatment.

- Using a multi-model approach.
- Being open-minded, patient and optimistic.

One area of concern is the fact that, since autism is such a complex disorder with still a lot of unknowns, this encourages the development of scams, pseudoscientific, and exploitative treatments. Despite the above fact, one still must remain open-minded. Some pseudoscientific therapies, if given with love, enthusiasm, and delivered in a manner that fosters optimism, may be more effective than a conventional and 'proven' therapy that is delivered in a cold, pessimistic manner, owing to the placebo and nocebo effects. Even pseudoscientific therapies sometimes may have an important wedge of truth, though that truth is overblown and exaggerated. The famous French author Voltaire, once observed: *"Il semble que toute superstition ait une chose naturelle pour principe, et que bien des erreurs soient nées d'une vérité dont on abuse."* The translation is: "It seems that underlying all superstition, there is a natural principle but errors are borne out of a truth that is abused" (Voltaire. *Essai sur Les Mœurs et L'Esprit Des Nations*. P445).

I worry about scientific inquiries that ignore a line of research simply because it is novel. In the case of autism, we must try to investigate everything we can about the disorder but from different aspects. There needs to be collaborative research efforts from various health care systems. While visiting MIT many years ago, I learned that researchers in computer science and technology were amazed to be able to solve a complex problem in a timely manner that they had been struggling with for some time. Although each field had solved bits and pieces of a complex problem, by combining the two fields, new answers were formed and with much greater accuracy. Researchers had also temporarily set up makeshift pods close to each other that allowed convenient brainstorming sessions. The same applies with autism. Different medical paradigms must break down their barriers and communicate with each so that new more effective solutions can be found.

The Illusion of a Quick Fix Solution and the Time Element

When it comes to finding a quick-fix solution for a medical disorder, this is possible only if one can identify the right set of triggers and correct them immediately using the most appropriate interventions available. The problem is that this usually does not happen. If one is exposed to a virus, for instance, it may start to replicate and elicit an immune response several days or weeks before symptoms are noticed. If detected very early, one may be able to abort the infection before it ever becomes a problem. In the case of autism and other neuropsychiatric disorders, not only is the initial insult not picked up early in most cases, but various secondary problems develop before the diagnosis is even made, making the initial insult somewhat elusive to treatment. By the time the symptoms are finally recognized and therapy is begun, one has to correct various secondary disturbances that have developed in addition to the initial problem.

Therefore, a quick fix should not be the goal of treatment in most complex conditions as it is often not possible. Although a quick fix may not be possible, I argue that full restoration should be sought even though time and effort may be required. The concept of patience has become all too foreign to us today. Restoration is possible when the right elements are present, but it takes time. The element of time may be a significant missing link in some situations. Each therapy should be given an appropriate amount of time to be effective.

To summarize, full restoration is possible with the right approach (using a biopsychosociospiritual approach), time, and patience.

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Dr. Jean-Ronel Corbier is a board-certified pediatric neurologist, based in the Carolinas, who sees patients from all over. He earned his medical degree from Michigan State University and neurology training in Cincinnati with additional training at University of Michigan, the Mayo Clinic, and Johns Hopkins Medical School. Born in NYC, Dr. Corbier moved with his parents to Africa and did missionary work in several countries for several years. Dr. Corbier has been recognized for his work with autism and has been invited to speak at national conferences on this topic. He has authored several books including three on autism (see http://www.brainrestorationclinic.com/resources/media/).

Dr. Corbier is founder and chair of a nonprofit organization, *Brain Restoration Ministries* (see www.brainrestorationministries.com). This NPO provides free clinical care to indigent patients and supports innovative neurological research.

For more information about Dr. Corbier and his practice, go to www.brainrestorationclinic.com.

Mast Cell Activation – Another Elephant in the Room

by Neil Nathan, MD

Over the years, my practice has slowly evolved to specialize in treating those patients who are unusually sensitive and/or toxic. These are the patients who react profoundly and for long periods of times (days or even weeks) to taking a single drop of a homeopathic remedy or a tiny dose of a supplement or medication.

The first step in treating these patients is to make a clear diagnosis. Experience has led me to the realization that the majority of these patients have mold toxicity, and many have Lyme disease and co-infections (particularly *Bartonella*) as well. Often, by treating these illnesses, we find that the extreme sensitivities to medication, chemicals, light, sound, touch and EMF slowly improve or resolve. However, sometimes I encounter difficulties in even beginning the treatment process, as my patient's ability to take *anything* that will get them started is severely compromised. My unfortunate patients are literally between a rock and a hard place. I know what they need to do, but they just cannot do it.

So, just when you thought it couldn't get too much more complicated, just treating Lyme and mold toxicity, with the profound, inter-related and interconnected, persistent inflammation that affects literally all of the systems of the body...doesn't that seem like more than enough? Indeed, the complexity of mold toxicity coupled with a wide variety of chronic infections is more than most physicians are willing to take on.

When a patient presents with the wide array of symptoms, which fluctuate in unpredictable patterns, such as intense anxiety and depression, severe pain (which can localize to joints, muscles, tendons, and bone), unusual neurological symptoms (like numbness and tingling in different parts of the body, paralysis, seizure-like activity), headaches, ringing in the ears, sensitivity to a wide variety of stimuli (light, sound, touch, food, chemicals, and electromagnetic waves), sore throat, swollen lymph glands, indigestion (including diarrhea, constipation, bloating, gas, distension, and heartburn), chronic, debilitating fatigue, insomnia, cognitive difficulties ("brain fog", decreased focus, memory and concentration), pelvic pain, interstitial cystitis, shortness of breath, air hunger, skin rashes, and difficulties with equilibrium – the mere breadth of symptoms is overwhelming and intimidating to patients and medical providers alike.

The most obvious medical response to someone who presents with these symptoms is "no one could have all of these symptoms; this must be in in your head." We should not be surprised that the vast majority of these unfortunate individuals are immediately treated as if this litany was psychosomatic, and they are dismissed with a prescription for an anti-depressant or anti-anxiety drug with the clear message given to them: "I can't help you. You need a good psychiatrist." And, the vast majority of these patients, while they personally doubt this diagnosis, cooperate with their physicians and see psychiatrists who duly provide these medications with minimal benefit.

Years pass. They do not get much better; in fact they get worse. If they are lucky, they find a Lyme-literate physician (LLMD) who tells them that yes, there is something that can explain all of these symptoms, and treatment often helps to varying degrees. With a little more luck, their physician is familiar with mold toxicity, which also can explain these symptoms; and they get better yet. Sometimes, they recover completely.

But some patients remain so sensitive to medications that every substance they try – be that a pharmaceutical prescription, herbal supplement, homeopathic remedy, acupuncture, electrical stimulation – makes them worse.

The good news is that we have recently realized that there is another elephant in the room: mast cell activation.

By understanding what this is, and, most importantly diagnosing it, we can provide additional treatment that will allow our suffering patients to improve and to move forward with treatment.

So, what are mast cells, and why should we care about them? Mast cells are an integral component of our immune system. While not present in large numbers, as are the better-known white blood cells such as neutrophils, lymphocytes and monocytes, they function as a critical *bridge* between the immune system and the nervous system. This bridge is not merely a metaphoric connection, but an actual, structural bridge that directly connects these two systems. I find it quite fascinating that many mast cells in the body are

connected, both directly (by abutting on nerve cells most notably branches of the vagus nerve) and indirectly by released chemicals, to the nervous system.

This implies that mast cells are vitally important as a coordinator between the two systems. It turns out that they are, indeed, and their basic function (among many others) is to coordinate the immune system's activities in dealing with toxins and infections. Ah, so the very agents that we have been focused on, toxins and infections, require functional mast cells to engage the body's natural defense systems.

Mast cells are present in every tissue of the body, but they are present in largest numbers in those tissues of the body that come into closest contact with the outside world. Well, that makes sense since, if you are going to coordinate dealing with toxins and infections, it is those tissues that will be asked to deal most directly with toxins and infections: namely, the tissues that line the sinus, throat, gastrointestinal tract, respiratory tract, skin, and genitourinary tract.

Mast cells are capable of making over 200 biochemical mediators (substances that convey signals to other cells and tissues that they need to be alert to incoming problems) in response to a wide variety of stimuli. When you look at them under a microscope, what draws your immediate attention is that they are loaded with tiny round dots, called "granules." Some of these granules contained pre-formed materials to quickly initiate these signals, the main ones being histamine, serotonin, and tryptase (among others). While all of these mediators can be important, histamine is the most obvious in terms of what it can do to the body if inappropriately stimulated.

So, when a mast cell is *appropriately* stimulated by a toxin or infectious agent, it can immediately release some of these granules which move quickly through the blood stream to coordinate a proper immune response.

However, when a person's immune system is overloaded with toxins or infection and their personal biochemistry and genetics align to create a "perfect storm," the mast cells become ***activated***. Other words that help us to understand "activation" would include hyper-reactive, over-excited, fragile, or trigger-happy. What I am hoping to convey is the sense that when mast cells do become overly reactive, they lose the specificity of their response; and they can now start reacting to ordinary stimuli that would not normally engage their attention. Now, foods that were once easily consumed, light, sound, touch, smells, and chemical exposures can trigger the sudden release of histamine and other substances that can, in moments, create havoc in the body. To put it simply, now our patient's body has become sensitized to such an extent that **almost anything** can cause an unpleasant reaction. At times, I have seen patients who react to drinking a glass of water with an intense histamine response.

This is where uninformed family members, friends, acquaintances, even physicians, look at our suffering patient and start to think: "That is impossible. No one can react to drinking a glass of water." But they can. And do. I know, at first glance it seems almost crazy, but when you come to realize that there is a true cause for this reaction, that it is not psychological, we come to see this very differently. What we have now, is an individual who has become so reactive that they do not know what direction their next assault is coming from. They often resist eating or drinking anything, as they cannot be sure what will have a debilitating effect on their body.

I want to emphasize that mast cell activation is a real, physiological process. And as I hope you can immediately see – it is frightening, chaotic, random and very hard to deal with.

Here comes the first kicker: it is often *triggered* by mold toxicity and/or infections like Bartonella and Lyme disease, as well as a wide variety of viral infections.

Many patients have a genetic predisposition to mast cell activation; but whether or not it manifests (ever) in their lifetime depends to a large extent on their exposures and how well their immune system functions.

And here comes the second kicker: it is not rare. While we have only recently begun to understand it, it is estimated that it may be present to some extent in up to 10% of our population. With the exposures that I see, in my practice, I would estimate that perhaps 50% of my ultra-sensitive patients have a mast cell activation component. It is, therefore, important that we understand how mast cell activation may reveal itself to us and what we can do to treat it.

Symptoms of Mast Cell Activation

If you are wondering why we are just now discovering how prevalent and how important mast cell activation is, let me take a few moments to explain. Given individual genetics and chemistry, and the fact that mast cells can produce over 200 different biochemical mediators depending on the stimulus they are exposed to, there are an astonishing number of symptoms that mast cell activation can produce. So much so, in fact, that like mold toxicity and Lyme disease, physicians have for years missed this diagnosis because they could not wrap their heads around the varied way in which this can present. I also believe that we are seeing this now in epidemic form because we have not recognized how toxic our world has become; and this, too, has sensitized many individuals to a greater extent than we are prepared to acknowledge.

In his ground-breaking book *Never Bet Against Occam: Mast Cell Activation Disease and the Modern Epidemics of Chronic Illness and Medical Complexity*, Dr. Lawrence B. Afrin has laid this out in wonderful detail. I would like to utilize his method of taking the body, system by system, and showing how each system may be impacted by mast cell activation, but I will try to do so in a somewhat simpler form.

I also want to emphasize how these symptoms may fluctuate and vary. They can be chronic or flare up for no obvious reason. Since histamine release is a common result of mast cell activation, some of the more obvious symptoms will be mentioned first, as these begin the process of drawing our attention to the possibility of diagnosis more quickly. I will again direct your attention to Dr. Afrin's books and articles for a more comprehensive listing, but the ones below are the ones that I have seen most often in my sensitive patients.

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- **Gastrointestinal:** Reactions that occur *quickly* after eating or drinking – especially if they involve something that appears allergic in nature such as flushing, sweating, rapid heartbeat (tachycardia), itching, swelling of the tongue, wheezing – get our immediate attention. More specifically, abdominal bloating, gas, diarrhea, pain, nausea (often with vomiting) are commonly reported.
- **General**: Malaise, fatigue, temperature dysregulation, weight loss or gain.
- **Sensitivities**: Increase in sensitivity to chemicals (multiple chemical sensitivity) and food, light, sound, smell, touch, even EMF (ElectroMagnetic Frequencies) exposure are common.
- **Lungs**: Wheezing, shortness of breath, "air hunger" in which the patient feels like they can't take a deep breath but oxygen saturation measurements are normal, laryngitis, and bronchitis.
- **Skin:** Rashes of every description, especially ones that are itchy (pruritis), often triggered by taking a hot shower, associated with flushing and hives.
- **Sinus/Oral**: Post-nasal drip, sensation of frequent tickling in throat, congestion, sinusitis, rhinitis, and pharyngitis.
- **Cardiovascular**: Lightheadedness, weakness, dizziness, vertigo, syncope (fainting), palpitations, arrhythmias, chest pain, areas of swelling (edema) that move about, and high blood pressure. POTS (Postural Orthostatic Tachycardia Syndrome) is common.
- **Pelvic:** Pelvic pain, bladder pain, flank pain, cystitis, vaginitis, prostatitis, and unexplained inflammation of the pelvic region.
- **Musculoskeletal**: Diffuse, shifting muscle and join pain (resembling fibromyalgia) often responding poorly to the usual pharmaceutical treatments.
- **Neurological**: Headaches, numbness and tingling (paresthesias) often in areas of the body that are not often associated with specific nerve root irritation, tremors, tics, seizures, pseudoseizures, and dysautonomia.
- **Psychiatric**: Anxiety, often with panic attacks, depression, mood swings which are often labile, cognitive difficulties, including "brain fog" and difficulties with focus, memory, concentration and insomnia are common symptoms.

These are an impressive array of symptoms, yes? And keep in mind I have not included the entire gamut of symptoms known to be associated with mast cell activation in an attempt to keep it as "simple" as I can make it.

I would like to emphasize that although many of these appear allergic in nature, there is a distinct *difference* between immediate allergic events, which are mediated by IgE antibodies, and the sudden release of histamine and other mediators from activated mast cells. I think it is important to emphasize this difference to help us to think about the possibility of mast cell activation when the immediate knee-jerk response is to assume an allergic reaction. To give an example of this, while attempting to administer intravenous phosphatidyl choline to a very sensitive patient, within seconds of starting her IV, she felt "awful" and had a marked increase in her pulse rate to 112, broke out in a sweat and felt itchy all over (which we term "pruritis"). Some physicians would assume this was an allergic reaction to the intravenous phosphatidyl choline, but actually it was caused by the sudden release of histamine from mast cell activation.

While the release of histamine is a part of the activation of IgE-mediated allergic reactions, I think it is helpful to attempt to differentiate these two responses. Clinically for this patient, starting with Benadryl administration was very helpful rather than an injection of epinephrine which would be a later strategy.

Diagnosis of Mast Cell Activation Syndrome

I have good news and I have bad news. The good news is that we do have effective ways of treating mast cell activation, which we will get to shortly. The bad news is that making the diagnosis can be quite tricky, at times almost impossible.

The reasons for this difficulty in diagnosis are several. First of all, I have tried to emphasize that there are over 200 different biochemical mediators released from mast cells, under certain conditions, meaning that there is a vast array of things that theoretically could be measured to confirm this diagnosis. However, when mast cells are activated, the release of these mediators is so rapid that often these biochemical substances are in and out of the blood stream in minutes. Their effects may last much longer, but actually catching their elevation in the blood stream is difficult, indeed. Multiple measurements may need to be made, especially when patients feel their worst to catch these evanescent spikes in mediators. Many of these mediators cannot be accurately measured by routine testing and require specific cold centrifuges (not available from most labs) and immediate processing to even begin to be accurate.

Having said this, these tests have been shown to be of value in clarifying the diagnosis of mast cell activation:

- **Total serum tryptase:** A positive test would be above baseline or "normal" during or within 4 hours of a symptomatic episode;
- **Chromogranin A**;
- **Plasma heparin** and/or **histamine:** Dr. Afrin has shown that using a cold centrifuge in the measurement of histamine makes this test much more accurate;
- **Urinary N-methylhistamine;**
- **Urinary PGD2** or its metabolite **11-beta-PGF2-alpha;**
- **Leukotriene E4**; and
- **Antibodies to IgE** (anti IgE IgG) and **antibodies to IgE receptors** are not currently seen as being diagnostic of MCAS, but rather as a hint that perhaps there is autoantibody mediated mast cell activation present.

It can be of particular benefit if a biopsy of tissue has been obtained, to carefully examine, or re-examine that biopsy after staining it with **CD**

117 to look specifically at the mast cell population in that specimen.

Treatments will be especially relevant for patients who are genetically negative for KIT-D816V. That particular gene is strongly associated with the rare condition of mastocytosis; and if a patient is negative for that gene, it suggests that they may be a candidate to try the medication imatinib.

But even if you have obtained all of these studies, repeatedly, you may not be able to make the definitive diagnosis of mast cell activation.

However, if you treat it successfully, using the methods noted below, this is strong presumptive evidence that this is indeed the diagnosis and that you are treating it correctly. Dr. Afrin cautions that he personally needs to see objective evidence of mast cell activation before pursuing more extensive treatments.

Treatment of Mast Cell Activation Syndrome

There are many strategies available for treatment, and often combining these improves outcomes. I would like to stress again that each patient is unique and different and that there are no clear rules or algorithms that can be universally applied. It is important to keep patients hopeful and enthusiastic so that they will continue to try new treatments even when previous ones have set them back. Eventually, you are bound to find treatments that work. The basic principles of treatment are as follows:

1. Reduce the production of mediators from the mast cells. Most important here is to identify what is triggering the activation in the first place. In my experience, mold toxicity is the most common trigger, followed by the infection *Bartonella*, which is often a co-infection of Lyme disease. This should be a principal concern, as I have often found that by correctly treating these triggers, mast cell activation literally disappears. There are a variety of desensitization therapies that are very helpful in this regard. While one is doing this (identifying and treating the triggers) it is extremely helpful to quiet mast cell activation by using what are called "mast cell stabilizers."
2. Interfere with the mediators that are released so that they will have a less potent effect on the body.
3. Counter unavoidable effects of released mediators.

Exercise and Diet

I have found that about 50% of my patients with mast cell activation respond well to a low-histamine diet and the other half does not. Therefore, I encourage patients to go online and find a low histamine diet they can work with (these diets are quite restrictive and can be difficult) and try it for two full weeks. If there is no obvious response, there is no reason to continue it. Keep in mind that mast cell activation is not the same as food allergies. Food allergies are consistent: the same food will always provoke the same response. Reactions to foods with mast cell activation depend greatly on the state of activation. With flare-ups, virtually any food can provoke a reaction, and when quiescent, the same food may be well tolerated. As you can imagine, this is both confusing and frustrating for patients (and their allergists and other doctors) since they often can't get a good handle on what they can or can't eat. This very point, in fact, helps us to look at these variable reactions as suggesting the diagnosis of mast cell activation.

Keeping in mind that a high percentage of my patients with mast cell activation have it triggered by mold toxicity, most need to be on a low carbohydrate diet, as carbohydrates, especially simple sugars, feed mold and candida and we need to avoid it. The majority of my patients have already discovered, before they come to see me, that avoiding sugars and carbohydrate is helpful.

The main point I want to make about exercise is that it can provoke a worsening of symptoms for some patients. This is especially true in those with post-exertional malaise, a condition in which following exercise there is a clear worsening of fatigue and muscle pain that can last for hours or even days. Post-exertional malaise will not improve with persistent attempts to exercise, even when encouraged by well-intentioned family members and friends. It is a measure of energy reserves, which most of my patients don't have. So, although I encourage exercise, it is important that my patients monitor how much they can do that does NOT provoke a worsening when completed.

Supplements and Medications for Mast Cell Activation

Using the basic principles of treatment provided above, we can select different families of both supplements and medications that can help to stabilize mast cells and to prevent the histamine that is being released from having as profound an effect on body systems. Usually these materials are synergistic, meaning that using several, especially ones with different modes of action, can improve a patient's response significantly.

I will often start with three materials, easily obtained, to gauge a patient's response or reactivity. How they respond (or react) will inform me as to what to try next. Unfortunately, we have very little science or testing to help us to know which materials will work for which patients, so this comes down essentially to a trial-and-error process. The better our patients understand this, the easier it is for them to cooperate with treatment attempts. If they are not prepared for the possibility that any material they are given may make them worse, they may abandon treatment efforts prematurely.

I usually start with the natural material quercetin, which is in the vitamin C family. It is an excellent mast cell stabilizer. Most of my patients tolerate it well, but a few (I would estimate around 15%) patients will react badly to it in its usual dosage, which would be starting at 500 mg once a day, given 30 minutes before a meal. (***It is important to take it before putting food into the body because that way it can begin the process of stabilization of the mast cells before they may be adversely affected by eating***).

If 500 mg is well tolerated after several days to a week, I encourage

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my patients to slowly work up to 500 mg taken 30 minutes before each meal and at bedtime. If well tolerated, and helpful, this dose can be doubled. For those patients who react negatively to the initial dose of quercetin, I will try a much lower dose, using the product NeuroProtek LP (which contains only 40 mg of quercetin), and sometimes this is well tolerated while the other form and dose of quercetin is not.

The quercetin is helping to stabilize the mast cells so they will be less reactive, but it will not do so perfectly. Some excess amounts of histamine are likely to be released, and it is additionally helpful to use both H1 and H2 histamine blockers so that the released histamine will have less of an adverse effect on the patient. I usually start with Claritin, found over the counter, at 10 mg and recommend taking the first dose at bedtime, since a few patients find that it makes them sleepy. If this is going well, the patient may then try taking it again in the morning. Again, a few patients find that Claritin will make them worse. Dr. Afrin has discovered that often the worsening is not from the substance itself (loratidine) but from the extra materials ("fillers") mixed in to the capsule or pill. Some patients who react badly to this (and anything else I may prescribe) will do much better by having that same pharmaceutical made up in purer form by a compounding pharmacy.

Once we have determined that Claritin is helpful (improvement may be immediate or take up to two months) I move on to Pepcid (famotidine), which is an H-2 histamine blocker, starting at a dose of 20 mg taken at bedtime and increasing to twice a day if well tolerated. Some patients respond better to Allegra or Zytec as H-1 blockers, and some to Zantac as an H-2 blocker.

Neil Nathan, MD has been practicing medicine for 46 years, has been board certified in family practice and pain management and is a founding diplomate of the American Board of Integrative Holistic Medicine. With Dr. Rich van Konynenburg he did the ground-breaking clinical research which demonstrated the importance of methylation chemistry in chronic fatigue syndrome, and he has recently completed a study with Dr. Robert Naviaux on the metabolomics of CFS. He has written several books and hosted an internationally syndicated radio program/podcast on Voice America.

His current medical practice is the Redwood Valley Clinic in Northern California. He can be contacted most easily through his website www.neilnathanmd.com, through which consultations are available.

About 50% of my patients will note some improvement with one or more of these three materials, ranging from slight to major. Their reaction helps to inform me about what to try next. I find that some patients do much better with natural materials, some much better with pharmaceuticals, and some with both. If they react negatively to pharmaceuticals, I will focus my next efforts on more natural materials. Conversely, if they react poorly to quercetin, I may focus more on pharmaceuticals. Each patient is unique, and we have to pay careful attention to every reaction as it holds a clue as to what to try next.

Natural Substances That May Be Helpful

This is not intended to be a complete list, nor am I intending to focus on any particular supplement manufacturer, but I will provide specific product names of materials that I have found to be of particular value. The materials noted here simply represent my own personal observations and are not intended to be comprehensive, but a starting point for further treatment efforts.

1. Perimine (extract of perilla seed) is a blend of bioflavonoids including luteolin and rosmarinic acid, which has been of additional benefit for some patients. Starting with one capsule, 30 minutes before a meal, it can be increased to one before each meal.
2. DAO enzymes (DiAmine Oxidase), which helps to break down histamine, support the healthy degradation of histamine. Starting with one capsule, 30 minutes before a meal, it can be increased to 2-3 capsules before each meal.
3. Allqlear, derived from quail eggs, contains a tryptase blocker, (tryptase being another material released by mast cells). Taking one chewable 30 minutes before a meal, the dose can be increase to two before each meal.

With each patient being unique, the dosage for all of these need to be adjusted to response or reactions.

Pharmaceuticals That May Be Helpful

1. Ketotifen is an H-1 antihistamine and mast cell stabilizer and also a functional leukotriene antagonist giving it a variety of ways in which it can be helpful. It is available by prescription from compounding pharmacies. I usually start with small doses, often 0.5 mg capsules taken at bedtime, and slowly increasing the dose as tolerated. It is also available as eye drops (for patients with symptoms that are eye-related) as ketotifen fumarate, using one drop two to three times a day in each eye.
2. Cromolyn sodium, another excellent mast cell stabilizer, can be used in a variety of forms. It has long been used to help exercise-induced asthma as an inhaler, but the same 20 mg dosage used in an inhaler is not the same as the oral dose, available in 100 mg vials. Sometimes it is helpful to start with tiny doses of the oral vial and work up the dose as tolerated by the patient. It is also available as an ophthalmic solution for patients with eye symptoms and as a nasal inhaler.

As a family physician, there are treatments and medications that can be prescribed by hematologists and allergists that are beyond the scope of my practice; and I refer the reader to Dr. Afrin's excellent discussion of their usage in his books and published papers for more details.

Summary

We are just beginning to appreciate how widespread is the occurrence of mast cell activation. It should be considered in the diagnosis of every patient who presents with an array of symptoms from many organ systems, and especially considered in patients with mold toxicity and Lyme disease since I find these to be common triggers for mast cell activation. So, first of all, think about it as a diagnosis. Secondly, it is treatable, so patients do not need to feel helpless or hopeless as they suffer with complex, debilitating illness. They should seek out physicians who are aware of and knowledgeable about mast cell activation to achieve optimal benefits. ◆

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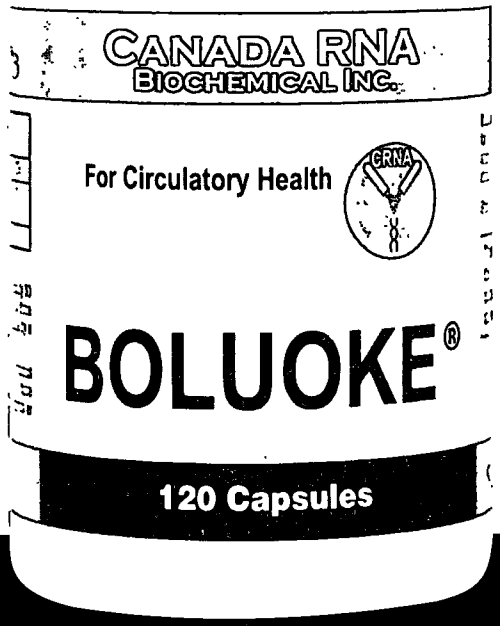

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Myelofibrosis – A Different Sort of Malignancy and a Case History of Control

by Davis W. Lamson, MS, ND

Tahoma Clinic, Tukwila, Washington

Introduction

Primary myelofibrosis is classified in oncology under myoproliferative neoplasms. Myeloproliferative neoplasms can demonstrate overproduction of one or more of the formed elements from the bone marrow and are said to be able to mimic one another.[1]

Myelofibrosis, along with polycythemia vera and essential thrombocythemia, comprises the BCR-ABL1-mutation negative members of a sub-group.[1,2] Of this group, myelofibrosis has the shortest survival time, with a mean estimate of six years. Pharmaceutical therapy has not been shown to be curative or disease modifying. Only stem cell transplantation has potential for cure or to prolong survival.[2]

Myelofibrosis is a genetic and metabolic condition (55-65% are accompanied by the gain-of-function JAK2 mutation), where fibrotic tissue begins to replace functional bone marrow.[1] The initial action can be a crowding out of bone marrow with resulting pancytopenia, abnormally low white blood cells, red blood cells, and platelets. It is not a classic malignancy in the usual sense.

The term "fibrosis" refers to excessive deposition of extracellular matrix, which then becomes fibrosis or scar tissue. Fibrosis is considered the cause of most organ failure.[3] It is driven by excessive transforming growth factor-beta and can involve genetic and epigenetic factors in the action pathway.[4–6] The condition can be reversed, if production is decreased.[3,7]

When the described patient arrived with diagnosis of myelofibrosis, the initial thought was to treat this like a fibrosis problem because of the known lack of success from other therapeutic concepts. At 83 years old, she would not be considered for stem cell transplantation. How control of myelofibrosis was apparently accomplished, with partial resolution of pancytopenia and complete elimination of the projected weekly transfusions for maintenance, is described and discussed below.

Significant History from Medical Reports Prior to Consultation

June 2013: Atypical lymphocytosis "consistent with chronic lymphocytic leukemia" (CLL). Further results showed deletion at 13q and no deletion at 17p. "13q gives a more favorable prognosis for CLL."

September 2016: Bone marrow biopsy comments: Chronic lymphocytic leukemia (10% involvement); JAK2 mutation positive, marked reticulin fibrosis, consistent with myeloproliferative neoplasm, such as primary myelofibrosis.

October 2016: Diagnosis of primary myelofibrosis with transfusion dependent anemia, thrombocytopenia, and leukopenia.

Consultation History

Visit 1 (10-13-16): Female, 83 years old with diagnosis (Dx) of CLL six years ago, with present Dx of primary myelofibrosis for three weeks. Requires RBC transfusion almost weekly. This is delivered by self-demand when hemoglobin tests low. The patient had been instructed how to recognize symptoms of low hemoglobin and would then report in for CBC and receive transfusion. Record of complete blood count varied widely because of maintenance by transfusion.

The patient had physical and lab signs of intestinal malabsorption and was instructed in gluten avoidance without lab diagnosis. Testing for gluten intolerance was not performed, as from the nature of the diagnosis and the frequent transfusions, a reliable result seemed unlikely. Testing was arranged for transforming growth factor-beta (TGF-beta) and prescription given for metformin-ER, 500 mg twice daily, and quercetin, 1000 mg twice daily.

Visit 2 (10-20-16): Astaxanthin, 12 mg twice daily, was added. Highly absorbed quercetin (as a "caged" molecule) was obtained from Tesseract Medical and provided after the visit (1/4 teaspoon, about 600 mg, containing about 105 mg quercetin).

Visit 3 (12-8-16): Patient showed the results of spontaneous bruising and bleeding under the skin, a likely outcome of her platelet level of 70. Vitamin K2 (15 mg daily as MK4) and

berberine (500 mg twice daily) were added. After the addition of ¼ teaspoon daily of the "caged" quercetin to the treatment regimen, the patient went 19 days without requiring transfusion, more than twice as long as previously. Caged quercetin was now increased to twice daily.

Visit 4 (1-5-17): Patient is now requiring only one transfusion per three to four weeks. Continuing on a program of regular quercetin (1000 mg twice daily), ¼ teaspoon caged quercetin twice daily, metformin-ER 500 mg, and astaxanthin. (Miscommunication resulted in TGF-beta not being tested until after the lowering agents were in place, and it was not elevated.)

Visit 5 (2-15-17): Patient has had some degree of diarrhea for a while. (A full stool culture was ordered and showed a 4+ growth of *Klebsiella pneumoniae*. Antibiotic treatment resolved the diarrhea.) Vitamin K2 was increased to 15 mg twice daily. Last transfusion was five weeks ago.

Visit 6 (3-13-17): No transfusion has been required since January. (This status has continued through June 2017, over five months.) The patient furnished a copy of her supplement list that included metformin-ER (500 mg twice daily), quercetin (1000 mg twice daily), Tesseract quercetin (1/4 teaspoon, about 600 mg, containing about 105 mg quercetin twice daily), berberine (500 mg twice daily), vitamin K2 (MK4, 15 mg twice daily) and a number of nutritional supplements used before treatment began for myelofibrosis. Quotation from oncologist report of 3-17-17: "Clear benefit from alternative therapy provided by Dr. Lamson at the Tahoma Clinic with transfusion independence." See Figure 1 for the compete blood count history. Transfusion dates after the first consultation were as follows:

- 10-12-16,
- 10-21-16 (nine-day interval),
- 11-19-16 (29-day interval),
- 12-9-16 (20-day interval), and
- 1-11-17 (26-day interval and last transfusion).

From the series of blood counts, the erythrocyte and platelet counts are stabilized and increasing with the present program, but the leukocyte level has increased into the abnormal range, both granulocytes and lymphocytes. A shift back toward the previous leukemia seems illustrated. Further, the shift has been rapid, and it is not yet known whether the leukocyte level will arrest near the previous high level and progress in the usual indolent CLL fashion or if this condition has become more aggressive.

Consultation with the medical oncologist will be obtained. One obvious approach, tapering the doses of the agents employed, could determine if a more favorable balance of erythrocytes and leukocytes is possible.

Discussion

Fibrosis is a "common pathway to organ injury and failure."[8] It seems chiefly driven by TGF-beta (transforming growth factor-beta).[9] Excessive TGF-beta results in deposition of more extracellular matrix, which can become fibrotic tissue. TGF-beta normally limits cell production, but changes in epigenetic or genetic factors can remove the limitation and result in over-production of affected cells and further increase TGF-beta.[10] Fibrosis is a reversible phenomenon and lowering TGF-beta can decrease it.[4] There are many publications reporting on the decrease of fibrosis in kidney,[11] lung,[12] liver,[13] etc. Searches of PubMed revealed at least 20 natural agents reported to do this. Unfortunately, there are no comparisons on degree of effectiveness.

On the basis of these findings, several agents were applied for the reasons described. Metformin has several anti-malignant actions, including in the hematopoietic area[14–17] and can attenuate organ fibrosis.[18] Astaxanthin can quench hydroxyl radical and possibly slow further DNA mutation.[19] Quercetin has many anti-cancer mechanisms and is known to lower TGF-beta and reduce fibrosis.[20–22] Further quercetin can inhibit the JAK/STAT cascade of inflammation and cell proliferation.[23] Berberine contributes to lowering the mTOR pathway implicated in myelofibrosis.[24,25] The vitamin K2 (MK4)

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Figure 1. Complete Blood Count History

Date	RBC	WBC	Abs Neut	Abs Lymph	Platelets
6-21-07	5.2 (H)	13.2 (H)	6.3	6.2 (H)	377
12-22-12	4.6	24.5 (H)	15.0 (H)	7.9 (H)	362
6-5-13	Dx of CLL				
2-9-15	4.8	19.4 (H)	10.6 (H)	7.5 (H)	328
6-8-15	4.9	17.3 (H)	10.6 (H)	5.6 (H)	259
11-30-15	5.0	15.7 (H)	9.4 (H)	5.5 (H)	195
4-21-16	4.0	15.2 (H)	7.1 (H)	6.5 (H)	80
9-12-16	Dx primary myelofibrosis with anemia				
10-13-16	Tx began at Tahoma Clinic				
10-25-16	3.3 (L)	8.3	5.3	2.0	62 (L)
11-2-16	2.7 (L)	8.0	5.3	2.0	69 (L)
11-4-16	3.3 (L)	7.2	4.3	2.4	57 (L)
11-29-16	3.2 (L)	9.4	5.8	2.9	65 (L)
12-6-16	2.8 (L)	11.0	6.7	3.3	70 (L)
12-13-16	3.4 (L)	10.2	6.3	3.0	53 (L)
12-20-16	2.7 (L)	10.2	7.1 (H)	2.4	56 (L)
12-30-16	3.0 (L)	10.9	7.2 (H)	3.0	54 (L)
1-3-17	3.3 (L)	12.8 (H)	8.4 (H)	3.7	71 (L)
1-9-17	2.9 (L)	12.8 (H)	8.5 (H)	3.7	71 (L)
1-24-17	3.6 (L)	15.3 (H)	10.3 (H)	4.1	99 (L)
1-31-17	3.5 (L)	15.5 (H)	10.6 (H)	4.1	110 (L)
2-7-17	3.5 (L)	15.5 (H)	6.5	3.0	101 (L)
3-28-17	3.7 (L)	16.3 (H)	11.1 (H)	4.4 (H)	89 (L)
4-18-17	3.7 (L)	15.3 (H)	11.0 (H)	3.4	92 (L)
6-9-17	3.9 (L)	20.9 (H)	---	5.5 (H)	121 (L)

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was added because of spontaneous bleeding from low platelets and the reported benefit to myelodysplastic syndromes and leukemias.[26]

A search of PubMed indicates that this may be the first report illustrating control of myelofibrosis with refractory anemia (other than stem cell transplantation) and by mostly non-prescription agents. Questions that remain are whether this program will continue successful over a long period, whether it will apply to other patients, whether it will extend lifespan, and whether it acts for the presumed reasons. (There are pathways that encourage fibrosis other than TGF-beta as well as other pathways operated on by the agents employed.) Further, it should be mentioned that serum TGF-beta is not a reliable indicator of cellular TGF-beta (p. 959).[27]

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Davis W. Lamson, MS, ND, practices at Tahoma Clinic in Tukwila, Washington with chief interests in autoimmunity and cancer. He has published research and reviews on hepatitis C, controlling MRSA, stimulating immune function, emphysema, autism, diabetes, gastroesophageal reflux, kidney failure, autoimmunity, and various cancer-related topics.

Dr. Lamson was adjunct faculty and coordinator of oncology education for 17 years at the Medical School of Bastyr University and supervised ND medical students in a hospital oncology setting.

Dr. Lamson received the 2004 Bastyr University Distinguished Alumnus Award and the 2005 President's Award of the Oncology Association of Naturopathic Physicians on its founding. In 2015, he received the Lifetime Achievement Award of that association.

Has the Cause of Psoriasis Been Found?

by Jonathan V. Wright, MD

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Jonathan V. Wright, MD's *Green Medicine* (Vol. 1, Issue 2, April 2016)

- Psoriasis is caused or aggravated by *Helicobacter pylori*
- Psoriasis can be eliminated or improved by *H.pylori* eradication

"Finding the cause" is the very necessary first step to a safe, effective solution to any health problem. Unfortunately, that first step is almost always ignored by the "standards of care" in much of today's medicine. Those "standards" routinely recommend one or more of thousands of patent medicines (also known as "drugs" or "pharmaceuticals") for nearly any health condition, even though it's perfectly obvious that no health problem has ever been caused by a deficiency of patent medicines! Duh!

Psoriasis has traditionally been a "disease without a known cause." As you likely know, psoriasis is characterized by plaques of red skin, most often covered with silver-colored scales ("plaque"), which are often itchy and painful, sometimes cracking and bleeding. According to WebMD,[1] "Although you can't cure psoriasis, there are ways to ease its symptoms."

Nature's medicine can help those with psoriasis. Many natural treatments involve overall lifestyle changes, which are thought to work by enabling the body to overcome whatever it is that's really the cause of psoriasis. The most effective natural treatment I've seen is nickel dibromide, which has helped clear psoriasis in most – though not all – individuals who've tried it. Nickel dibromide (sold as Psorizide Ultra) was developed by Tulsa dermatologist Steven A. Smith, who published a 1997 article about it.[2]

Although Dr. Smith wrote that bromide had been found to work against the overly rapid growth of skin cells involved in psoriasis, what caused skin cells to grow excessively rapidly was still not clear.

Three publications appear to have brought us closer to the actual cause. Here are the titles of two of these three publications:

- "Complete remission of palmoplantar psoriasis through *Helicobacter pylori* eradication: a case report."[3]
- "Clearance of chronic psoriasis after eradication therapy for *Helicobacter pylori* infection."[4]

These two publications are just single-case reports. However, it's not unheard of for a single case to be the basis for a major shift in medical thinking and treatment. The "single case" discovery that *H. pylori* could cause peptic ulcers was the first step on the road to the 2005 Nobel Prize in Physiology for Australian internist Barry J. Marshall and his colleague J. Robin Warren.

The third publication implicating *H. pylori* as a causative factor in psoriasis[5] was based on examination and testing of three hundred individuals with psoriasis plaque. All of those – 100% – diagnosed with psoriasis judged "moderate" or "severe" had positive tests for *H. pylori*; 37% of those with "mild" psoriasis were *H. pylori* positive. Treatment to eliminate the *H. pylori* was just as effective as conventional patent medicine treatment in improving or eliminating psoriasis.

While it's still too soon to conclude that *H. pylori* is the root cause of psoriasis, it appears to be at least a major factor. If you or anyone you know has psoriasis, why not have testing done (perhaps the "*H. pylori* breath test") to see if *H. pylori* is involved? If it is, please be aware that "standard of care" treatment for *H. pylori* can have some nasty adverse effects. Please make sure to check with a physician skilled and knowledgeable in natural medicine for effective but much safer natural treatment for *H. pylori*, which according to these three reports will likely improve or eliminate psoriasis!

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Cannabinoid Deficiency and Its Impact on Human Health and Disease, Part 4

by Jonn Desnoes, OMD, MD, PhD, and Sandra Kischuk, MSMIS, MCPM

Adverse Effects, Drug Interactions, and Contraindications

In reviewing 31 medical marijuana trials, Borgelt, et al noted that researchers reported 4,779 adverse events in patients receiving a medicinal cannabinoid for 8 to 12 months. Of these, 96.6 percent events were not serious (most common: dizziness - 15.5%). There were 164 serious events, the most common being multiple sclerosis relapse (12.8% of the events), vomiting (9.8% of the events), and urinary tract infection (19.1% of the events).[1]

Other mild-to-moderate adverse effects included "somnolence, ataxia, blurred vision, headache, dry mouth, sedation, dizziness, conjunctival irritation/ dry eyes, hypotension, feeling intoxicated, nausea, and difficulty with concentration and/or memory." Most of the reported adverse effects are typically not serious, with the most common being dizziness.[1]

But, what of the effect of exogenous (outside) cannabinoids on the brain?

A study by Giovanni Battistella, et al investigated brain structure changes in a group that smoked cannabis on a regular basis and a group that smoked it only occasionally. All subjects were between the ages of 19 and 21, had no psychiatric disorders, used only cannabis – no other drugs, and were split into two groups based on age of first cannabis use, in order for the investigative team to evaluate effect of cannabis on the developing brain[2]:

> In normal adolescents the volume of cerebellar gray matter starts to decrease around puberty and continues to do so until early adulthood ... (probably) due to the pruning of the (unused) synaptic connections ... (by) endogenous cannabinoids.[2]

This may be the first study showing temporal pole gray matter atrophy in regular cannabis users with the degree of atrophy directly correlated with drug use frequency three months before the study began, as well as medial temporal cortex changes (a common finding associated with cannabis addiction and regular cannabis use). However, another possibility is that abnormal pruning may result from a genetic predisposition: The researchers would have no way of knowing whether the brain changes were present before or were the result of cannabis use.[2]

This study on the effects of long-term exposure to cannabis on brain structure integrity found the following:

- An association between regular cannabis-reduced gray matter volume in cannabinoid-CB1-receptor-rich regions "functionally linked to motivational, emotional, and affective processing";
- A correlation between the magnitude of these changes and frequency of cannabis use; and
- The magnitude of these changes was modulated by the age at which an individual started smoking cannabis.[2]

Of interest is that past studies have shown that the body may be neuroadaptive: Cognitive changes and CB1 activity may become normal after a period of cannabis abstinence. The researchers could not reach a conclusion as to whether the structural changes were permanent or temporary and recommended longitudinal studies.[2]

One of the things we need to remember is that what we have today "ain't your mama's marijuana." Over the past 40 years, cannabis growers have concentrated on increasing the THC content and reducing CBD because a better "high" meant more money for the grower. CBD steps down the psychoactive effect of THC, which is of no help if you are trying to get high or trying to sell a premium psychoactive product. Since CBD is attracted to both CB1 and CB2 receptors, it may also serve in a protective capacity. THC is close to a perfect fit for the CB1 receptor. CBD (cannabidiol) is not a perfect fit for either the CB1 or the CB2 receptor; "it stimulates both types of receptors without actually binding to them."[3]

Project CBD research has shown that CBD counteracts the psychoactive effects of THC by inhibiting its effects on CB1 receptors. CBD also causes an increased release of 2-AG, one of the endogenous cannabinoids. Like CBD, 2-AG stimulates both CB1 and CB2 receptors, which enhances the overall effect on the body. Studies published by the National Institutes of Health have shown that cannabidiol also inhibits the activity of fatty acid amide hydroxylase, or FAAH. This slows the deterioration of anandamide,[3] the aforementioned "bliss" endocannabinoid.

Psychiatric Issues

Marijuana's chief psychoactive component, THC, is an agonist of the CB1 receptors, which function to modulate appetite, mood, and motivation. An individual's response to marijuana depends on dosage level, the strain of marijuana, and frequency of use. Typically, marijuana will induce "mild euphoria, sedation, relaxation, hunger, and enhanced sensory input." It will also impair "attention, balance, cognition, judgment, memory, and sense of time." Some less fortunate users experience "anxiety, disorientation, paranoia, and psychosis." A higher relative level of cannabidiol may be protective

and reduce the frequency of psychotic symptoms.[1]

Cannabis use does not cause schizophrenia, but adolescents who use marijuana heavily can have earlier onset of and double the risk of developing this chronic neurodevelopmental disorder. Ongoing use of cannabinoids after the onset of schizophrenia increases psychosis severity, fragments attention, and makes impulse control difficult, if not impossible.[1] Physiologically, cannabis use interferes with adolescent neurodevelopment, with imaging studies showing compromised hippocampus and cerebellum maturation.[1]

Cannabis use is associated with memory and cognition impairment; heavy use, in particular, is associated with deficits in the encoding, storage, and retrieval of memory. The latter correlates with the visible brain structure atrophy in memory areas: the amygdala and hippocampus. Typically, executive function, information processing, and visuospatial perception suffer with marijuana use.[1]

Researchers have found a modest association between frequent cannabis use and depressive disorders, impulsivity, and suicidal ideation and attempts. And there are concerns about dependence:

> Cannabis is the most commonly used and abused illicit substance in the world. In the United States each year, approximately 6500 individuals begin to use marijuana daily, of whom 10–20% will develop cannabis dependence. Among people admitted to substance treatment facilities in the United States, marijuana is the most frequently identified illicit substance.[1]

Pediatric Issues

Calls to the National Poison Data Center have increased with the increased availability of medical marijuana. Symptoms of acute cannabinoid toxicity include such neurologic symptoms as "decreased coordination, decreased muscle strength, lethargy, sedation, difficulties concentrating, altered psychomotor activity, slurred speech, and slow reaction time ... tachycardia, and dry mouth." Pediatric patients may exhibit more severe symptoms such as apnea and cyanosis. Common symptoms include ataxia, somnolence, lethargy, altered mental status, severe hyperextension, and spasticity. Although no deaths related to marijuana have been reported to national poison centers, there can be significant morbidity.[1]

The increased availability of cannabinoids increases the risk for exposure in children and adolescents, which often results from consumption of cannabis-laced foods. This is complicated by the lack of safety or regulatory packaging. Best practice for cannabis products, as for all prescription and over-the-counter drugs, is to always secure drugs in a safe place with child-proof locks.[1]

The Entourage Effect

In 1999, Raphael Mechoulam co-authored a paper with Shimon Ben-Shabat, et al, "An entourage effect: inactive endogenous fatty acid glycerol esters enhance 2-arachidonoyl-glycerol cannabinoid activity," that changed the way cannabis researchers would approach future studies. Mechoulam administered the endocannabinoid 2-AG (2-arachidonoylglycerol) with two related inactive compounds to mice. The result? The 2-AG endocannabinoid bound more easily at the receptors, and the mice exhibited a greater behavioral response than when 2-AG was used alone.[4]

Scientists had searched for years to find *the* active chemical component in cannabis. What Mechoulam, et al, discovered was that certain compounds, which themselves were biologically inactive, facilitated and enhanced the effect of active components, and that the presence of these inactive constituents could alter the results from those observed when the active component was applied in isolation.[4] In Mechoulam's words:

> Biologically active natural products, from either plant or animal origin, are in many instances accompanied by chemically related, though biologically inactive, constituents. Very seldom is the biological activity of the active constituent assayed together with the inactive 'entourage' compounds. In view of the results described above investigations of the effect of the active component in the presence of its 'entourage' compounds may lead to observations of effects closer to those in Nature than investigations with the active component only.[4]

In 2001, John McPartland and Ethan Russo published a paper, "Cannabis and Cannabis Extracts: Greater Than the Sum of Their Parts?" in the *Journal of Cannabis Therapeutics*. In this work, they applied the "entourage" concept to the cannabis plant itself, noting "Good evidence shows that secondary compounds in cannabis may enhance the beneficial effects of THC ... Cannabis terpenoids and flavonoids may also increase cerebral blood flow, enhance cortical activity, kill respiratory pathogens, and provide anti-inflammatory activity."[5]

A decade later, Russo substantiated the molecular-teamwork hypothesis and expanded on it in a paper published in the *British Journal of Pharmacology*, "Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects," which contains an amazing 304 citations.[6] At a Fall 2010, Israeli-sponsored medical conference, he discussed the role of "minor" phytocannabinoids, including tetrahydrocannabivarin, cannabigerol, and cannabichromene, in synergistically enhancing the therapeutic effects of THC and CBD. His presentation also covered evidence that "phytocannabinoid-terpenoid interactions" enhanced the therapeutic effects of cannabis.[6]

Cannabinoids, themselves, are odorless. Terpenoids, which are made up of repeating 5-carbon molecule chains (isoprene), provide fragrance in aromatic bark and wood, citrus peel, and smelly herbs (eg, sage, mint). Researchers now suspect that these very volatile and very potent terpenoids (of which there are over 200 in cannabis) may have a role to play in providing synergistic support and biofunctional enhancement of cannabinoid benefits. In their 2001 paper, McPartland and Russo had gone so far as to explore the role terpenoids played in expanding the "medicine chest" cannabis provides, detailing the terpenoids that would most augment each of the cannabinoids in practical use.[5] The addition of terpenoids and flavonoids to the cannabinoid "medicine chest" complicates the genetic development of new strains of cannabis exponentially but impacts the potential for even greater therapeutic results.[7]

Conclusion

A century ago, medical science did not know of the existence of the endocannabinoid system or the role cannabinoids played in the health of the human body. No longer. D Sulak, in his discussion of the endocannabinoid system on the Norml website, dedicated to reforming marijuana law, noted, "The

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endogenous cannabinoid system, named after the plant that led to its discovery, is perhaps the most important physiologic system involved in establishing and maintaining human health."[8] Cannabinoid deficiency has consequences as insidious as any parasitic disease or cancer, laying low and silently destroying health for decades; as consuming as any bacterial or fungal enemy; and as treacherous as any virus hijacking its host's DNA.

The saddest fact is that the cause of this condition is man-made and politically induced. But, this is nothing new. Even in the 21st century, it is a fact that those who are not medical professionals can be jailed for practicing medicine if they provide advice on health issues, no matter how accurate or helpful. It is also well-known that proponents of alternative medical treatments are often hounded by the government until they willingly stop promoting their ideas, get arrested and incarcerated, or suffer financial destruction through the actions of its agents. Yet, how much of the "conventional" medical care people receive worldwide is dictated by political convenience, powerful individuals with "agendas," megalithic chemical corporations, and profit-crazed insurance companies? If I were not a medical professional, I could be arrested for recommending or denying appropriate medical treatment. Yet, every day, insurance companies decide what treatments patients can or cannot get. Is this not practicing medicine?

Even the government can decide, not only whether Medicare will or will not cover a procedure, but whether a patient can or cannot get a desired procedure, even if the patient is willing to pay for it out of his or her own pocket. Is it any wonder that in the years 2014 to 2016, *Forbes*, *Time Magazine*, *WebMD*, *NBCNews*, *CBS News*, and *The Washington Post* reported that the United States had the worst, most expensive healthcare in the developed world?

Greed, which stems from illogical, infantile, and irrational fear of privation; obsession with controlling others; and an unbridled hunger for power combined with medical ignorance produced legislation that should never have been enacted. The prohibition of hemp and its related compounds created consequences that have produced needless pain and suffering, unnecessary hardship, and the destruction of the lives of millions of people. The time is long overdue for this criminal act that has been imposed upon humanity to be reversed, and the injustice and needless suffering be brought to an end.

It is time we take a second look at what makes sense and move away from the hysterical "Reefer Madness" mindset. Cannabis has hundreds of chemical components, including some which are exclusive to that plant and that plant alone. We already know of the powerful effect of some of these on treating pain, inflammation, and even cancer. We need to look more closely at everything this plant has to offer and to make it available to those people whose lives it can rebuild and restore. To do anything less is inhumane. To deny hope for a cure is evil.

If we can clarify a complex, emotionally and politically charged subject using unbiased, science-based information; if we can enlighten minds with facts and a new understanding of how the human body works; and if we can demonstrate the wisdom of using a simple God-given plant our bodies were designed to use to restore health; then perhaps we can set in place legislation that is fair and sensitive to peoples' needs, that does not place profits above human welfare, and that frees people from unnecessary pain and disease.

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Sir Jonn Desnoes, OMD, MD, PhD, is a physician, board-certified homeopath, former nationally syndicated radio talk show host, writer, researcher, and medical missionary. He was knighted for his humanitarian work as a medical missionary.

Jonn became interested in the study of cannabis and its health-restoring properties when a friend gave him a bottle of CBD hemp oil. He had suffered with intractable back pain for years as a result of multiple sports injuries incurred over 30 years as an athlete. Within 20 minutes of taking the CBD oil, his excruciating pain stopped. He has found that, as long as he continues to take the oil, he is virtually pain-free.

Dr. Desnoes may be reached by email at drjonn@mac.com. His website is askdrjonn.com.

Sandra Kischuk, BSBA, MSMIS, MCPM, is a writer, editor, life coach, Toastmaster, and master gardener. Author of *Fighting the Dragon: How I Beat Multiple Sclerosis*, Sandra's writing interests include fiction, non-fiction, poetry, scripts, and other people's résumés. She has written web content for physicians, informational/marketing literature for attorneys, and continuing education courses for dental professionals, and edited professional communications and doctoral theses on subjects as diverse as religion, education, engineering, and psychology.

The "Retracted" Studies

There are no long-term studies that have compared overall health of totally non-vaccinated children to those who are fully vaccinated as defined by the CDC schedule. The US Institute of Medicine noted this lack in its 2013 report "The childhood immunization schedule and safety: Stakeholder concerns, scientific evidence, and future studies." Although drug interaction and overdose are accepted realities in medicine, the CDC continues to add new vaccines and extra doses of older vaccines to the childhood schedule despite evidence that adjuvants in some vaccines have adverse neurological and immunologic effects.

Comparing vaccinated to unvaccinated children in the US has been problematic because most of the population has been at least partially vaccinated; the number of never-vaccinated children is so small in general population samples that detecting rare, but serious, adverse effects is impossible.[1] Withholding vaccines from children to act as a control for long-term studies is considered unethical. Professor Anthony R. Mawson and colleagues at Jackson State University (Jackson, MS) teamed up with Brian D. Ray, President of the National Home Education Research Institute (NHERI), to see if a population of homeschool children might include sufficient numbers of vaccinated and never-vaccinated children to provide a statistically viable means for comparison. Homeschoolers are known to have lower vaccination completion rates.

The Mawson pilot study was published by the peer-reviewed *Journal of Translational Science* in April 2017, along with a second study involving a subset from the pilot study. The pilot study compared the health of vaccinated and unvaccinated homeschool US children, ages 6-12.[2] The second study reported associations between preterm birth, vaccination, and neurodevelopmental disorders.[3] As is typical of epidemiologic studies, Mawson and colleagues used chi-square tests, odds ratios, and 95% Confidence Intervals in evaluating their null hypothesis: "If the effects of vaccination on health were limited to protection against the targeted pathogens as is assumed to be the case, no difference in outcomes would be expected between the vaccinated and unvaccinated groups except for reduced rates of the targeted infectious diseases."

With Brian Ray's help, Mawson and colleagues contacted statewide homeschool organizations in Florida, Louisiana, Mississippi, and Oregon and asked them to forward an email to their members that explained the study's purpose and provided a link to an online survey. The researchers were not looking for a representative sample of all homeschool children in the US. Rather, they sought a "convenience sample of sufficient size to test for significant differences in outcomes" for this pilot study.

Qualtrics, a marketing research software company, hosted the online survey website for three months in the summer of 2012. Respondents were asked to consent to participation, give their zip code and state of residence, and confirm that they had biological children between ages six and 12. In addition to demographic information and child vaccination and health history, the questionnaire also asked about confounding factors such as the use of antibiotics, acetaminophen, alcohol, and antacids during pregnancy, gestational diabetes, preeclampsia, Rhogham shot during pregnancy, and whether they lived near a hazardous waste or manufacturing site. The survey questionnaire consisted of yes-no, closed-end questions. "Financial incentives to complete the survey were neither available nor offered."

The survey gained 415 completed questionnaires, providing data on 666 homeschool children: "...261 (39%) were unvaccinated, 208 (31%) were partially vaccinated, and 197 (30%) had received all of the recommended vaccinations." As expected, the incidence of chickenpox and pertussis was significantly less in the vaccinated group; "but, contrary to expectation, [the vaccinated children] were significantly more likely to have been diagnosed with otitis media, pneumonia, allergic rhinitis, eczema, and neurodevelopmental disorders [ADHD, autism spectrum disorder, learning disability]," write the authors. Partially vaccinated children "had an intermediate (apparently detrimental) position in terms of allergic rhinitis, ADHD, eczema, and learning disability." In the adjusted analysis, neurodevelopmental disorders (NDD) were significantly associated with vaccination (OR 3.1, 95% CI: 1.3, 6.8); male gender (OR 2.3, 95% CI: 1.2, 4.3); and preterm birth (OR 5.0, 95% CI: 2.3, 11.1).

The second published study investigated a possible association between preterm birth, vaccination, and neurodevelopmental disorders. None of the children who were born preterm and remained unvaccinated (n=12) had a neurodevelopmental disorder. The authors found that vaccination, not preterm birth itself, was associated with NDD: "...vaccination coupled with preterm birth was associated with increasing odds of NDD, ranging from 5.4 (95% CI; 2.5, 11.9) compared to vaccinated but non-preterm children, to 14.5 (95% Ci: 5.4, 38.7) compared to children who were neither preterm nor vaccinated." Preterm infants are routinely administered vaccines according to CDC schedule at two, four, and six months after birth, regardless of gestational age.

The authors admit the limitation of the small sample in this report and say more studies are needed: only 51 of the 666 children in the original study were born pre-term and 50 of the 666 had a neurodevelopmental disorder. But they say the link between vaccination in preterm infants and neurodevelopment disorder is biologically plausible:

> Receipt of one or more vaccines could precipitate NDD in some preterm infants by exacerbating a preexisting inflammatory state associated with prematurity, leading to hepatic encephalopathy and hypoxic-

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ischemic brain damage. Impaired liver function is a predisposing factor for preterm birth and the latter is associated with increased risks of hypoxic-ischemic brain injury.[3]

The Mawson studies were nearly never published – not because of scientific flaws or misconduct but because journals did not want to deal with the controversy, pushback, and smear that the results would attract. In the Q&A after his presentation at the 2017 Autism One conference,[4] Dr. Mawson explained that the study had originally been accepted by the peer-reviewed journal *Frontiers in Public Health* but was then rejected before publication. Rejected, not retracted as Retraction Watch falsely claimed. An online post of the study's abstract drew the ire of those who view anything that questions vaccine safety as being "anti-vaxx." Celeste McGovern reports a tweet from Leonid Schneider claiming credit for getting the study pulled: "'I pride myself to have caused the Frontiers anti-vaxx retraction with one tweet! The anti-vaxx paper was published as abstract, a reader alerted me, I tweeted, Frontiers got scared, pulled the paper.'"[5] Whether or not Schneider's tweet was fully responsible, *Frontiers* backtracked and declined to publish the full study.

Mawson said a second journal, hearing about the Retraction Watch claim that the study had been retracted by *Frontiers,* immediately returned the study. *Journal of Translational Science* (JTS) accepted the study; but upon hearing about *Frontier*'s "retraction," this journal also pulled it. Retraction Watch falsely claimed that Mawson's study had been retracted a second time. At this point, Dr. Mawson sought legal advice; "retraction" indicates scientific misconduct, a serious charge. The lawyer sent a letter to *JTS*, clarifying that the study had *never* been retracted. So, *JTS* published the studies. Dr. Mawson emphasized this is a pilot study, a preliminary step in determining whether this line of research is worth pursuing. Funding is required to do a necessary and larger one.

There was a time when controversial results were tested with additional studies by independent researchers. Now, it seems, smear campaigns and censorship rule – at least in the area of vaccines.

We have learned a tremendous amount about neurodevelopment and the immune system since the smallpox vaccine was first used two hundred years ago, and not all vaccines have the same risk-benefit for every person. Yet, the CDC continues to add vaccines to the schedule as if they were all benign, magic bullets against disease. Meanwhile, the integrity of any practitioner or researcher who questions CDC vaccine policy is trashed by smear-mongers, who whether from ideology or personal profit, prefer to leave the growing vaccine schedule unexamined and unchecked.

From my perspective, media is doing everything it can to ignore these questions and maintain the status quo: the widely disseminated belief that any and all vaccines provide vital health benefits that outweigh any risks. Vaccination is being treated like an issue of religion: dogma vs. heretics. The problem is that government agencies are forcing that dogma on parents and practitioners. Government agencies in Australia, Italy, Romania, and California are requiring full vaccination in order for children to attend school. In some cases, parents can lose government financial aid, must pay a fine, or face the intrusion of child protective services if they do not comply. California doctors who give medical exemptions because of a family history of autoimmune disorders or patient history of an adverse reaction attract attention from the state medical board.

Do we really want health safety issues to be determined by smear campaigns, propaganda, and censorship?

Jule Klotter

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Can CAM Docs Legally Prescribe and Sell Herbals and Nutritional Supplements as Therapy Without Bad Things Happening?

Many CAM (complementary and alternative medicine) and integrative doctors recommend and/or sell all kinds of nutritional and herbal products to their patients. There is a supplement manufacturer sub-industry that only sells to physicians and other health care professionals, for resale to patients. And most of the top tier, high profile docs have their own private label supplement brands. That's a fact. But is it legal and ethical to do so?

Legal is a matter of state law. But for better, (but mostly) for worse, ethical is largely determined by those noble, public-spirited and never ethically-challenged folks at the AMA (American Medical Association for those living under a rock). They're not completely controlled by Pharma; just ask them and they will tell you. And they're not trying to stop cheaper non-patentable interventions like nutritional supplements and herbs, all at Pharma's behest. Their thought leaders do not receive tens, hundreds of thousands, or millions of dollars from Pharma for research, public relations, and advocacy. Just ask them and they will tell you.

And their "ethical guidelines" reflect an open-minded attitude serving the best interests of the patients. Okay, you get the point.

So, is it "AMA ethical" for physicians to sell nutritional and herbal products? Technically yes, but practically, not so much. Here's the latest iteration of the AMA "ethical" rule on the sale of health-related products. (Sorry, it's longish)

> 9.6.4 Sale of Health-Related Products The sale of health-related products by physicians can offer convenience for patients, but can also pose ethical challenges. "Health-related products" are any products other than prescription items that, according to the manufacturer or distributor, benefit health. "Selling" refers to dispensing items from the physician's office or website in exchange for money or endorsing a product that the patient may order or purchase elsewhere that results in remuneration for the physician. Physician sale of health-related products raises ethical concerns about financial conflict of interest, risks placing undue pressure on the patient, threatens to erode patient trust, undermine the primary obligation of physicians to serve the interests of their patients before their own, and demean the profession of medicine. Physicians who choose to sell health-related products from their offices or through their office website or other online venues have ethical obligations to:
> (a) Offer only products whose claims of benefit are based on peer-reviewed literature or other sources of scientific review of efficacy that are unbiased, sound, systematic, and reliable. Physicians should not offer products whose claims to benefit lack scientific validity.
> (b) Address conflict of interest and possible exploitation of patients by: (i) fully disclosing the nature of their financial interest in the sale of the product(s), either in person or through written notification, and informing patients of the availability of the product or other equivalent products elsewhere; (ii) limiting sales to products that serve immediate and pressing needs of their patients (e.g., to avoid requiring a patient on crutches to travel to a local pharmacy to purchase the product). Distributing products free of charge or at cost makes products readily available and helps to eliminate the elements of personal gain and financial conflict of interest that may interfere, or appear to interfere with the physician's independent medical judgment.
> (c) Provide information about the risks, benefits, and limits of scientific knowledge regarding the products in language that is understandable to patients.
> (d) Avoid exclusive distributorship arrangements that make the products available only through physician offices. Physicians should encourage manufacturers to make products widely accessible to patients.

So, what does this gobbledygook mean? *Well, it means that you CAM docs have a problem.*

First, virtually no supplements or herbal remedies have the kind of scientific support set out in subparagraph (a). There are only a few supplements for which the FDA have approved health claims, like folic acid for pregnant mothers, and such. I also suspect that the peer-reviewed literature the rule refers to means mainstream journals to the AMA. My guess is that this AMA subsection could be used to render "unethical" the recommendation of the products routinely recommended and sold by physicians. *But there are bigger problems.*

Subsection (b) seems to suggest you have to either give away the products, or sell them at cost in order to avoid the conflict of interest or appearance of the conflict. Moreover, you're only supposed to give away or sell at cost enough product to meet the patient's immediate needs, or until they can get the product from a less conflict-ridden source.

This is idiotic. By the logic of this provision, if you go to a surgeon for a surgical consult, it would be unethical for the surgeon to actually perform the surgery rather than just recommend it because he has a financial interest in performing the operation.

But not to worry, under the rule, the surgeon can lessen the conflict by either 1. Operating for free, or 2. Charging his actual cost, rather than the high fees the surgeon normally charges. To further lessen the conflict, he should only do a temporary surgery, just fix the problem enough to allow

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the patient to go to another surgeon who has no financial conflict of interest arising from the first surgeon's surgery recommendation. The same would apply to an interventional cardiologist recommending a stent, angiogram/angioplasty, or to any other physician who both makes recommendations and provides a procedure or therapy to effectuate or implement the recommendation.

To generalize, there is the same conflict of interest for any professional who both consults and does something. By the logic of the AMA rule, a lawyer cannot both recommend suing and actually suing (unless he sues for free or at cost). Nor could a lawyer prepare a trust, or do anything the lawyer recommends because implementing the recommendation means that the lawyer makes extra money for the doing, which under the logic of the AMA rule irreparably taints the lawyer's judgement (unless the service is done for free or at cost, and is only a temporary fix until a conflict-free professional is retained).

The AMA world view embodied in this rule reminds me of the commercial for a personal identity protection company. You know these commercials: There's a patient with his mouth open in a dentist's chair, and a guy with a white coat looking in the patient's mouth who says "You have one of the worst cavities I've ever seen." The patient says. "OK, doc, fix it." And the guy in the white coat says "Oh, I'm not a dentist; I don't fix teeth, I'm just a dental monitor."

In the AMA la-la ethical world, the guy tells the patient "Yes, I am a dentist and I'd like to fix your tooth, but I have a conflict because I'm going to make extra money doing what I said should be done. So, we're done here, and you have to see another dentist who will actually fix your cavity"

Is this really how we want physicians who have a service or product to act? Have them become health care monitors and have another class who are health care problem fixers?

Let's not leave AMA ethical la-la land yet: At the new dentist's office, the dentist looks over the films, examines the patient, and concurs with the recommendation, thereby creating a chargeable evaluation and management fee. Doesn't the new dentist also have a conflict? He's got his examination fee, and he'll get extra money for fixing the cavity. This can get ridiculous!

Let's face it, we rely on professionals to give their opinions and implement a solution within their expertise. This happens zillions of times a day, all over the world. To single out physicians who use and sell the kind of products used by millions of people is just nuts.

This rule obviously hasn't been used to stop surgeons, cardiologists, or dentists from doing the thing they were trained to do. But what about a CAM physician who uses herbals or nutraceuticals as primary therapy? Can they do that, or are they caught in the same AMA ethical net?

But before we get to that, here is another question: Does this AMA ethical rule matter? Short answer: yes. A little longer answer: It matters because some state medical board laws have specifically incorporated the AMA ethical rules into their standards of professional conduct, such that a violation of an AMA ethical rule is a violation of the state's medical board law. Even in the absence of express incorporation, states can and do go after physicians for ethical violations of all sorts (just ask docs like Burzynski about that).

Why is any of this relevant or important to CAM docs? There's a new case against a doc (it's my case, and not in California or Texas where I maintain offices, but I don't want to give the details just yet), which raises the very issue of whether it is unethical and a state board law violation to use and sell herbal and nutritional interventions as primary therapy. What makes the case more interesting is that the therapy is only available from physicians, and only physicians who have gone through the company's training about how to use the products. (Many of you CAM docs probably know the product line I'm referring to.)

How can the AMA possibly view this kind of thing as the "sale of a health-related product?" Well, maybe it doesn't, but initially at least, the state medical board seems to think it is the sale of a "health related product" and is going after the doctor for doing so.

Here's where it gets interesting with the AMA ethical rules: The second opinion after the sale of health-related products is the following ethical precept:

> 9.6.6 Prescribing & Dispensing Drugs & Devices In keeping with physicians' ethical responsibility to hold the patient's interests as paramount, in their role as prescribers and dispensers of drugs and devices, physicians should: (a) Prescribe drugs, devices, and other treatments based solely on medical considerations, patient need, and reasonable expectations of effectiveness for the particular patient. (b) Dispense drugs in their office practices only if such dispensing primarily benefits the patient. (c) Avoid direct or indirect influence of financial interests on prescribing decisions by: (i) declining any kind of payment or compensation from a drug company or device manufacturer for prescribing its products, including offers of indemnification; (ii) respecting the patient's freedom to choose where to fill prescriptions. In general, physicians should not refer patients to a pharmacy the physician owns or operates. AMA Principles of Medical Ethics: II,III,IV,V.

Does this section apply to a doctor prescribing and selling a product used as primary therapy if the product is only available from the health care provider and only from one who is trained by the manufacturer? It seems to. Although the heading only refers to "drugs" and "devices," the actual rule specifically mentions "drugs, devices, and other treatments."

A prescription is just a written order issued by a healthcare provider containing the provider's recommendation for a

product, such as a drug, device, or other treatment, or in some cases a recommendation of behavior (like bedrest). So a written order by a physician to take an herb or nutritional supplement in order to cure or mitigate a disease is a prescription and such products are prescribed. (And in case you are concerned, the fact that a physician prescribes an herb or supplement for the treatment of a disease doesn't turn the product into a drug because it's the manufacturer's intent that governs not the prescribing practices of healthcare providers, under FDA law.)

Admittedly, the language in (b) mentions a pharmacy but not all prescribed things are found in pharmacies. Take the aforementioned bedrest for example. And we're stipulating that the prescribed products can only be obtained through the doctor and are not available directly to the consumer.

So, does this AMA rule 9.6.6 sanction a physician prescribing an herbal remedy or supplement for the treatment or mitigation of the disease or medical condition? I looked at the literature and haven't seen any cases on this yet. I think it does, and the case I'm working on will provide what may be the first legal ruling on the issue.

As a backup, it seems to me that even if both AMA ethical rules could apply, I don't see how a medical board can sanction a physician for a violation of an ethical rule where the physician's actions are ethical under another ethical rule, or arguably so. It seems to me that a board must first make this determination, publish it, and put the licensees on notice, which my research indicates has not yet been done in this state at least.

So, although I think I am right, as of right now, there doesn't appear to be a definitive answer to the question as to whether a CAM physician can prescribe and sell an herbal remedy or nutritional supplement or supplement regime as primary therapy for the treatment or mitigation of a disease, at least in a state which has specifically incorporated the AMA ethical rules. But give me six months or so and I'll give you the answer; hopefully the one you're looking for.

In the meantime, and to make that happen, any academics out there with some ethics background care to opine and help make it happen? I'll be waiting to hear from you.

Rick Jaffe, Esq.
rickjaffeesquire@gmail.com

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Adaptogenic Herbs

review by Donald A. Carroll, OD, NT

Adaptogens in Medical Herbalism – Elite Herbs and Natural Compounds for Mastering Stress, Aging, and Chronic Disease
by Donald R. Yance, CN, MH, RH(AHG)
ISBN 978-1-620551004; 2013; 672 pages; kindle, $29.49; hardcover, $34.83.

"Donald Yance knows more about molecular oncology than any oncologist I know, with perhaps the exception of myself," states Dwight L. McKee, MD, CNS, ABIHM, and a diplomate of the American Board of Medical Oncology. Dr. McKee also states that, "Although I have studied botanical medicine intensively for the past five years, I have no hope of ever matching Donnie's expertise, which he has refined from more than twenty-five years of intensive study."

With that introduction, don't you think that his science-backed book on how herbs and nutrients can master the stress, aging, and chronic disease should be in everyone's library interested in pushing the envelope on the last frontier of medical herbalism? I have studied most of the leading natural medicine practitioners. I always come away with questions such as, "Why do you treat low thyroid with porcine-based thyroid instead of trying to heal and support the thyroid? Why do you suggest taking bioidentical hormones for menopause just because a woman is no longer having a menstrual cycle?" I know that the endocrine system and how it relates to the immune system, the nervous system, and the hormone system is very complicated, but now we have direct evidence on how to treat the whole complex system with herbal adaptogens and nervines (herbs that therapeutically work on the nervous system). This book has educated me beyond anything I have ever read on how herbs work and why they are safe to use in relatively high dosages daily without serious side effects like drugs have. Yance is a master herbalist and knows how to combine the herbs in a synergistic manner to get maximum therapeutic effect for every condition.

The book begins with a history of herbal medicine and how it evolved into pharmaceutical drugs as we know them today. The author shares his own holistic approach, called the *Eclectic Triphasic Medical System*, which he based on extensive scientific research, more than 25 years of clinical practice, and excellent results with thousands of patients. Emphasizing spirituality, exercise, and diet in addition to herbal treatments and nutritional supplements, Yance's complete lifestyle program explores how to enhance energy production in the body and subdue the proinflammatory state that lays the groundwork for nearly every degenerative disease.

Yance shows how adaptogenic herbs modulate the immune system and can potentially master the autoimmune diseases so prevalent today. Then he details how adaptogenic herbs combined with nervines nourish the nervous system providing the foundation for optimal thinking and memory. There are many chapters going into all of the details of how it all fits together along with over five thousand references to studies. The last part of the book is a monograph of all of the important herbs he recommends. It is like an encyclopedia of the medicinal herbs.

As an optometrist, I closely monitor diabetic patients each year to make sure that they are not starting to get diabetic retinopathy. It is amazing how many studies have been done to show how to lower blood sugar with herbs alone. The primary adaptogens – such as American ginseng, Manchurian spikenard, rhodiola root, and eleuthero – improve insulin utilization and balance and strengthen the hypothalamic-pituitary-adrenal (or HPA) axis.

Holy basil and devil's club, which are secondary adaptogens, also have insulin-trophic actions. Yance lists the many other herbs that are helpful: bitter melon, cinnamon, fenugreek seed, goat's rue, gymnema leaf, Indian kino, and salacia. Goat's rue is the basis for the antidiabetic medication Metformin, a drug widely used in the treatment of Type-2 diabetes mellitus. Indian kino demonstrates some very unique features, which include beta-cell-protective and beta-cell-regenerative properties, as well as blood-glucose-lowering activity. Indian-Kino extract has shown an ability to reverse damage to beta islet cells and actually repopulate the islets. *The herbs actually help the pancreas to heal besides lowering the blood sugar.* How many drugs do that?

In another study, we actually find that salacia is a more potent glucose inhibitor than acarbose, a commercial alpha-glucosidase inhibitor found in diabetic medications. Salacia as a tea had an inhibitory effect that lasted 110 minutes, significantly longer than any tea tested. Salacia has also been found to inhibit aldose reductase, an enzyme normally present in the eye and in other parts of the body that facilitates the transformation of glucose into a sugar alcohol called sorbitol. Too much sorbitol trapped in eye and nerve cells can damage these cells, leading to neuropathy.

I had one of my own questions answered about the thyroid. A whole chapter on thyroid explains that when building one's vital essence with adaptogens, endocrine issues dramatically improve, and problems such as hypothyroidism often disappear. For thyroid support, Yance uses shatavari, rehmannia, chaste tree, royal jelly, ashwagandha, guggul, nettle, and schisandra along with nutritional agents such as N-acetyl tyrosine, vitamin D, iodine in form of bladder wrack, and natural selenium at 200 micrograms. Now that is true healing, since by taking porcine-based thyroid your thyroid actually gets weaker; you are not helping your thyroid.

If you want to finally be able to understand how the dynamics of thriving plays out, I don't think you will ever need another book. This book puts everything else to shame. As far as I am concerned, it is the definitive treatise. I tell my patients if they followed everything in this book, their ills would disappear and they could begin to experience life's exciting journey. Yance connects you with the healing agents of nature that have all of the natural molecules we need to even change our genes into truly functional engines reflecting a real *joie de vivre*.

By the way, I have first-hand experience using his herbal tinctures and it has taken my health to an all new level of vitality, vibrancy, and vivaciousness. Now after entering my senior years, I feel better than when I was in my forties. ◆

The Sunshine Hormone

review by Donald A. Carroll, OD, NT

The Miraculous Results of Extremely High Doses of the Sunshine Hormone Vitamin D3 – My Experiment with Huge Doses of D3 from 25,000 to 50,000 to 100,000 a Day over a 1-Year Period
by Jeff T. Bowles.
ASIN: B005FCKN2S: July 18, 2014; 196 pp; kindle, $2.99; paperback, $9.95.

Author Jeff Bowles has clearly devoted thousands of research-hours to provide cutting-edge information about Vitamin D3 in a book that has sold more than 200,000 copies; 60,000 in Germany alone since it was released in August 2011. The book has been translated into German and Polish and is now being translated into French, Spanish, and Portuguese. You can check the reviews for yourself and see that I am not alone in truly appreciating this healing book. At last count, there were 667 reviews on the US Amazon website, 250 on the UK Amazon, and another 250 or so on the German Amazon website. People are excited and eager to share.

Not only has he documented a tremendous amount of scientific research but Jeff has used himself as a human model in his own studies on using doses of D3 far higher than normal. He claims this simple vitamin, also obtained from the sun, can cut healthcare costs by 90%. I have to agree.

The work noted in Jeff's self-published e-book is an amazing real-life, human trial that has helped thousands of people to try their own experiment with taking a higher dose of Vitamin D3. We have all been told not to take too much D3; that it is dangerous. Jeff, a research scientist, investigated all of the scientific studies on D3 and could find no substantiating research that indicated that it was harmful even in high doses, unlike Vitamin D2, which is. Jeff decided to start out on 25,000 IU of D3 and ended up taking 100,000 IU a day. He found a great deal of benefit with the high doses but found out that once he was sufficient with D3 that 10,000 IU to 25,000 IU a day was enough to sustain the good benefits gained by "loading" the dose. The only side effects he noticed were the way his old bone injuries started to remodel from years past, and it was a little painful as it progressed. He learned, by experimentation, to lower the dose if it became too painful because the bone remodeling was progressing too fast.

The main thing Jeff's book documents is that in his research he noted nearly all of the broad spectrum of diseases were improved with the high doses of D3. The other major point Jeff brings out in his research was that in high doses you also need to add Vitamin K2 to keep the calcium-regulating part of the hormone-effect of Vitamin D3 directing the calcium into the bone and teeth instead of the arteries and/or the joints.

Some of the chronic conditions Jeff personally had that were cured using the high doses of D3 were bone spurs, fungus toenail, a facial cyst, a ganglion cyst, arthritis, and he even lost 25 pounds. The story is fascinating and enjoyable. It motivated me so much that it made me feel as if I couldn't wait to try it myself for my own ailments. So, I did! I tried it, along with the recommended Vitamin K2, and could not believe all the benefits I received. What was most interesting in my own experiment with high-dose D3 was the healing of a very old malady of mine, Dupuytren's contracture in my hand, which had caused a hard knot and was in danger of deforming my fingers. It was amazing to first notice the recurrence of pain, which had been absent for years and years in the hand. But more amazing was to watch the hard knot slowly dissolving along with the pain and a freer motion in the hand than I'd had in years.

Since this was first published as a Kindle e-book, there have been thousands of people from all walks of life around the world who have responded online, sharing their success stories from using high-dose D3. Jeff emailed me a story from a person in Austria, knowing it might help me in my nutritional therapy practice as an optometrist. This man had lost his central vision in his left eye from a retinal vein occlusion. He was able to regain his vision in several weeks from taking 60,000 IU of D3 a day. In all my years of being an optometrist I have never seen or heard of a retinal vein occlusion repair like this. They usually result in a permanent loss of central vision. It is very exciting to see real-world beneficial responses from a book like this. That fortunate man has Jeff's thousands of hours in research, self-testing, and writing to thank for regaining his sight.

As a side note, I did a search on GreenMedInfo.com's advanced search engine and noted 180 different conditions with Vitamin-D3 deficiency as a contributing cause. Jeff's work in this arena will most likely have a positive impact on the majority of disease sufferers as most will fall within the category of one of the 180 conditions listed.

As an additional side note, www.vitamindcouncil.org offers in-home test kits for those wishing to have before-and-after measurements of their Vitamin-D3 levels. As we head into the darker months, it is an excellent time to read Jeff Bowles' superb book and begin to experience the resolution, as I did, of some long-standing health problems by simply taking supplemental D3.

Contact Dr. Donald A. Carroll, OD, NTP at donn.carroll@gmail.com; 360-951-2986

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Ted Rozema

Dr. Theodore Carl Rozema, 83, of Cuenca, Ecuador, formerly of Tryon, North Carolina, died on June 9, 2017. Born April 11, 1934, in South Haven, Michigan, he was predeceased by his parents, Martin and Alta Rozema, and his brother Steve Rozema.

Dr. Rozema is survived by his wife, Frances Greenway Rozema; former wife Marie Ewald Rozema; children Craig Rozema, Cara Keys and Carlyn Keylor and Tony Greenway; grandchildren, Matthew Keys, Rachel Rozema, Allison Keys, Reese Rozema, Caitlyn Keylor, Chaz Rozema, Alyssa Keylor, Jakob Greenway and Allen Greenway; and his sister Carol Knapp.

Dr. Rozema attended and graduated from Northwestern University Medical School and served his internship at Cook County Hospital in Chicago. He then served as medical doctor in the United States Air Force.

Ted came to the Landrum area in 1976, when he moved his family from Wadsworth, Illinois, to Tryon to establish a Paso Fino horse farm, Rancho del Rosa. Dr. Rozema opened up his medical practice in Landrum, South Carolina, in 1978, which later became Bio Genesis Medical Center.

Dr. Rozema lectured and taught in many countries. His teaching and professional experience include 53 years of clinical practice of medicine and 29 years of chelation therapy for metal toxicity. He was the past president of the American College for Advancement in Medicine, past president of the International College of Integrative Medicine, president of the American Association of Alternative Medicine, president of the Health Research Foundation and was a member of many other medical organizations.

Dr. Rozema authored numerous articles that were published in medical journals. One of the most prestigious was "The Protocol for the Safe and Effective Administration of EDTA and other Chelating Agents for Vascular Disease, Degenerative Disease, and Metal Toxicity" (*Journal of Advancement in Medicine.* January 1997;10(1):5-100). Dr. Rozema received numerous honors and awards from other countries for his participation and lecturing on chelation therapy.

In addition to his medical practice, he also owned and operated the Landrum Antique Mall. He loved the area and lived and worked here for many years as a respected member of the community. Later in life he decided to retire to Ecuador where he lived in Cuenca, Bahia, and lastly in Salinas. He will be remembered as a father, a brother, a husband, a doctor, a veteran, an author, a Paso Fino horse farm owner, an entrepreneur, someone who was constantly seeking knowledge, and a world traveler. He will be missed by his family and friends.

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Functional Gastroenterology Bolus

by Steven Sandberg-Lewis, ND, DHANP

Helicobacter pylori – Commensal, Pathobiont or Pathogen?*

Ever since the scientific community accepted the discovery by Marshall and Warren in the late 1970s, *H. pylori* has been met with a "test and treat" approach. The present doctrine is basically that "the only good *H. pylori* is a dead *H. pylori*." Martin Blaser, Director of the NYU Human Microbiome Program, and his research associates are among those who have studied both the pathological and the health-promoting effects of this important organism. Blaser's recent book, *Missing Microbes*, is must reading for healthcare professionals. Although it is clear that *H. pylori* colonization is associated with peptic ulcers, gastric adenocarcinoma, and gastric lymphoma (aka maltoma), there is evidence that it also is an "ancient dominion organism."

H. pylori is likely at the commensal center of the gastrobiota, the normal flora of the stomach.[1] Research reveals that it has been an inhabitant of the human stomach for nearly 60,000 years. All mammals have a species-specific Helicobacter, and these organisms may be essential for proper maturation of the gut immune system. Research speaks to this organism's role in prevention of reflux, Barrett's esophagus,[2] and esophageal adenocarcinoma[3]; asthma, eczema and rhinitis[4]; laryngeal carcinoma[5]; celiac disease[6]; Crohn's disease[7-11]; and possibly obesity.[12] It may also protect against fatal cardiovascular events.[13]

The term *pathobiont* is described by Janet Chow, et al:

> Although the mechanisms that mediate pathology remain largely unclear, it appears that genetic defects and/or environmental factors may predispose mammals to immune-mediated diseases triggered by potentially pathogenic symbionts of the microbiota. We have termed this class of microbes `pathobionts', to distinguish them from acquired infectious agents.[14]

Therefore, *H. pylori* may be best considered a commensal that can also transform into a pathobiont, a commensal with important immunomodulatory functions, especially in the neonatal and childhood periods of development.

The advent of prescription antibiotics in the early 20th century, increases in Cesarean births and decreases in breastfeeding rates, smaller family sizes, less crowding, and improved water and food sanitation have all decreased transmission of *H. pylori* to children.[15] Although no single antibiotic has been shown to eradicate the organism, Blaser suggests that repeated courses of single antibiotics may eradicate *H. pylori* in mice. While rates of Helicobacter colonization were originally nearly 100%, in the US only 6% of children have *H. pylori* colonizing the stomach. This may be one of several reasons why the incidence of allergic diseases, reflux, and its complications (including esophageal cancer), obesity, and certain autoimmune disease have dramatically increased in the latter 20th century.[16]

A theory is that altered gut microbiota lead to a "continuous antigenic stimulation" predisposing to autoimmunity. *H. pylori* colonization may inhibit this stimulation by activating regulatory T cells. Lack of colonization or early eradication of the organism in children may predispose to Crohn's disease, etc.

H. pylori is not just one organism but is very diverse in form[17] and has several adaptive features for life in the stomach: the enzyme urease to protect itself from acid by creating a cloud of ammonia, a corkscrew-like morphology that allows it to burrow into mucus, and "virulence factors" that allow it to interact closely with the host stomach to downregulate parietal cell acid production and many other functions.[18] CagA and vacA are the most studied of the virulence genes. I know of only one commercial lab that currently tests for these.[19]

CagA+ and vacA+ virulent strains increase the chance of hypochlorhydria and protect against the development of GERD. Helicobacter eradication in patients with pangastritis has been documented to cause reflux esophagitis. Eradication can also lead to recovery of ghrelin secreting cells and raise plasma ghrelin levels, which may predispose to obesity. It is important to consider the presence or absence of these virulence factors when reading the literature.

It is also important to consider the location of a patient's bacterial gastritis. Pangastritis (inflammation of the entire gastric lining) is associated with hypochlorhydria whereas antral predominant gastritis is associated with hyperacidity. The antrum is the site of G cells, which produce the acid-stimulating hormone gastrin. The gastric body is the location of parietal cells, which produce acid. When the antrum is inflamed, gastrin can be produced and the gastric body can respond with acid production. When pangastritis is present, the parietal cell mass in the gastric body is decreased and therefore less acid can be made in response to gastrin. The most useful *H. pylori* research will specify both location of the bacterial gastritis and the presence of virulence factors. Risk of gastric cancer is likely related to specific subtypes of *H. pylori*.[20]

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*I would like to thank Dickson Thom, DDS, ND, for introducing me to the idea of *H. pylori* as a commensal over a decade ago. We team taught the gastroenterology course at the National College of Naturopathic Medicine (now National University of Natural Medicine) for many years.

Helicobacter pylori

The clinical question to ponder is when to treat and when to give your patient a "high five" to celebrate the protective presence of this ancient dominion organism? Based on my study of this conundrum over the last two decades, I propose considering the following:

1. Strongly consider eradicating *H. pylori* when it is present in patients with documented gastric or duodenal ulcers or gastric lymphoma (maltoma). This approach significantly reduces ulcer recurrence and cures maltoma in over 80% of cases.[21]
2. When considering the risk for gastric adenocarcinoma, the risk is about 1% for patients with *H. pylori* pangastritis. This is the hypochlorhydric patient presentation and not necessarily the same patient that develops duodenal ulcers. None of this is settled science, but consider these facts when discussing treatment options with your patient. Note: One study showed that early treatment of *H. pylori* in gastric ulcer patients significantly reduced the risk of gastric cancer more than early treatment of duodenal ulcer.[22] This makes sense since gastric ulcer patients may have hypochlorhydria or achlorhydria whereas duodenal ulcer patients are more likely to be hyperchlorhydric.
3. Strongly consider avoiding *H. pylori* treatment in a patient who does not have the typical diseases associated with this organism. Stool, breath, saliva, or serum testing a patient suffering from functional dyspepsia or gastroesophageal reflux for *H. pylori* status also makes little sense, considering the protective effect of this organism against GERD and GERD-associated complications.

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Ask Dr. J

by Jim Cross, ND, LAc
thias1020@yahoo.com

The Answer Lies Within

Cat Stevens has a wonderful song called "On the Road to Find Out" from his *Tea for the Tillerman* album. The lyrics of that song defined my early 20s life, but one line from the end of the song defines my professional medical life: "the answer lies within." I believe that true health begins at a deeper level than just a superficial or pharmaceutical one. How deep one travels depends on the functional medical paradigm one chooses to follow.

The always interesting Sir Isaac Newton had a great line: "If I have seen a little further, it is by standing on the shoulders of Giants."[1] I was able to have an hour-long, three-way conversation with Eric Gordon, MD, and Bob Naviaux, MD, from the University of California-San Diego. Dr. Naviaux is an extremely interesting fellow. He directs a core laboratory for metabolomics at UCSD, is co-founder and a former president of the Mitochondrial Medicine Society, and is a founding associated editor of the journal *Mitochondrion*. The Naviaux lab at UCSD is focused on the study of mitochondria and their role in energy production, metabolism, and cellular defense.[2] I wonder if one of his influential songs was also "On the Road to Find Out"?

Dr. Naviaux has developed a concept called the cell danger response or CDR. It is amazingly similar to Bruce Ames' triage theory. Dr. Ames describes his triage theory thusly: "The triage theory posits that the spectrum of functions of a particular vitamin or mineral are managed by the organism such that, when micronutrient availability is limited, functions required for short term survival take precedence over functions whose loss can be better tolerated."[3] He proposed that a consequence of this evolutionary adaptation is an increase in the risk of chronic diseases of aging when vitamin/mineral availability is limited. The triage theory, then, is a hierarchy of priorities in the body, set by natural selection. To me, this intriguing theory describes why the standard American diet (SAD) allows Americans to actually survive their nutrient-depleted diet but, of course, not thrive on it.

The CDR is similar in concept but comes from a slightly different angle. It primarily involves what should be everyone's favorite cellular organelle: the mitochondrion. The mitochondrion is an extremely interesting organelle as it lies at the intersection of cellular energy creation, cellular energy management, and cellular waste management. Glucose is broken down in the cell's cytoplasm via glycolysis and in the mitochondrion via the Kreb's cycle and the electron transport system to produce the molecule of cellular energy, ATP. Due to the multitude of chemical reactions occurring every nanosecond in the .mitochondrion and its encounters with chemical, physical, and/or biological threats, it is susceptible to situations that exceed the cellular capacity for homeostasis. When this arises, then the CDR is set off. For various nutritional, environmental, genetic, and metabolic reasons, the CDR does not shut off in the present-day mitochondrion which leads to systemic disturbances such as disruption of the microbiome, derangement of whole body metabolism, multiple organ impairment, and changes in behavior.[4] Dr. Naviaux, then, is saying that environmental dangers can be defined biochemically in the cell. Basically, this constitutes what chronic disease appears to be: a derangement in the health and functionality of the mitochondrion! ➤

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The CDR was meant to be a temporary, stop-gap measure to deal with a short-term attack on the cell. After the attack has been neutralized, a very specific set of anti-inflammatory and regenerative pathways would then spring into action to deal with the cellular debris that had been created and to fix any cellular machinery that had been damaged.[4] Sounds perfect, yes? It is, but unfortunately we live in non-Paleolithic times where, due to multiple environmental contaminants, the CDR is not being turned off. This then leads to a suboptimal performance in mitochondria all over the body, which can manifest in a myriad of ways that were listed in the above paragraph. All of these manifestations appear to be the genesis of chronic disease. Cat Stevens was correct; the answer does lie within to reversing and eliminating chronic disease.

Now, of course, we have to have the scientific ability to diagnose what is happening to our cute little mitochondria and how to correct this imbalance, hopefully without pharmaceuticals. Dr. Naviaux has developed a metabolomics test that will measure the efficacy of multiple cellular biochemical pathways. He hopes to use this information to turn the CDR off near the beginning stages of a chronic disease instead of at an organ dysfunction level. His metabolomics test measures various metabolites of cellular metabolism. His test is at the heart of studies he is conducting on autism and chronic fatigue syndrome.

How cool would that be to have a real-time test that gives you a snapshot of your cellular biochemistry! Basically, Dr. Naviaux is choosing to measure compounds that don't quickly come and go in a cell but that are present the majority of the time. If we use the analogy of a tree with its trunk, branches, and leaves, these compounds would be the branches and not the leaves. The leaves are very vulnerable to even the slightest breeze, but it takes much more of a wind to move the branches.

His metabolomics test measures 61 biochemical pathways that he considers essential to seeing the big picture of how well the cell is working biochemically. These 61 pathways will give him a good, solid cross section of cellular biochemistry. The issue now is to interpret this panel for "healthy people." His lab has been studying certain groups of people with chronic diseases such as Gulf War illness, PTSD, and autism and appears to have worked out what is dysfunctional biochemically in their syndromes. Now, his lab is attempting to develop algorithms that will be able give useful clinical information on people who haven't progressed to serious chronic illnesses yet to determine what is happening biochemically in their cells and clinical steps to take to reverse their current dysfunctional biochemical directions. Truthfully, diseases like Gulf War illness and autism could be classified as cellular post-traumatic stress disorder due to their CDR not being turned off.

What is especially cool to me is that Dr. Naviaux is attempting to triangulate his metabolomic testing with exposures to environmental toxic exposures in a toxics panel. Let's take dioxin exposure as an example. A person with their own particular set of single nucleotide polymorphisms (SNPs) will react differently to the same amount of dioxin exposure as someone with another unique set of SNPs. Each person then will have a unique metabolomic pattern that will manifest over time in a slightly different manner. Said another way, everyone has their own unique cellular breaking point where the scale becomes tipped in a downward spiral of dysfunctionality. I think these ideas will, over time, lead to cogent explanations of why people in the same area with the same chemical/heavy metal exposure develop different patterns of illness.

This could well become true preventive medicine, but it also can become an arbiter of the success or failure of functional medicine treatments. Was it the herbs, the homeopathic remedies, the craniosacral adjustments, or stress reduction that helped a particular patient improve? With this metabolomic testing, we will not have to throw the kitchen sink at patients and hope that one or two of them stick. We can attempt just a few treatments at a time and see if the patient's metabolomic pattern improves. If so, stay the course. If not, try another modality and measure what it accomplishes or doesn't accomplish. Basically, this will validate effects of various treatments on illnesses, refine our treatments, and give us a better idea of what possible treatment(s) work(s) for what disease.

So, hopefully everyone's future will soon entail being able to have a lab produce a biochemical road map that shows their own particular dysfunctional cellular pathways and what therapeutic choice(s) can correct them. Mitochondria are the true canaries in the coal mine. If we can figure out what their cries mean, we will be able to reliably reverse and potentially cure many chronic diseases.

I want to end with Dr. Naviaux's sense that environmental degradation is at the heart of our current health crisis and the type of diseases that are manifesting. He wants the children of the world to grow up with the default knowledge that all life on earth is sacred and that, if we stay the present course, our families will soon be overtaken by disease and our national economy will collapse under this burden. Unfortunately, economic forces clash with environmental sustainability. Basically, immediate monetary gratification leads to long-term environmental un-sustainability. If we could only persuade the majority of citizens on our planet that Earth's health trumps corporate wealth!

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2. http://naviauxlab.ucsd.edu/
3. http://www.bruceames.org/Triage.pdf
4. Naviaux R. Metabolic features of the cell danger response. *Mitochondrion*. 2014 May;16:7-17

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Women's Health Update

by Tori Hudson, ND
womanstime@aol.com

Primary Care Issues: Fatigue and Osteoarthritis of the Knees

Vitamin D Can Improve Fatigue in Otherwise Healthy Individuals

Fatigue is a very common complaint in men and women, and can lead to obvious impacts on quality of life, work performance, home life, moods and more. There is a check-off list for fatigue, both in the history and in laboratory testing, that a clinician will use to assess possible causes that include anemias, hypothyroidism, depression, poor nutrition, protein deficiency, celiac disease, food or airborne allergies, blood sugar issues, poor or not enough sleep, and then a more serious investigation, if needed, into chronic diseases/cancers.

Vitamin D insufficiency or deficiency is common in the United States and has been associated with fatigue, headache, depression, muscle pains/weakness, impaired cognition and more. The current study investigated a single vitamin D dose to see if it improves fatigue after 30 days among individuals who were vitamin D deficient and had fatigue but were otherwise healthy.

This randomized double-blind clinical trial was conducted at the University of Zurich. Study participants with fatigue were enrolled and were between the ages of 20-50, of normal body weight, not suffering from other physical or mental illness, and had a serum vitamin D level below 20 mcg/L. Fifty-three percent of the participants were women. One hundred twenty-eight individuals were enrolled in the study, and a total of 122 participants underwent the baseline visit and took the study medication or the placebo.

The primary endpoint was intra-individual change in the fatigue assessment scale (FAS) at four weeks after the treatment. The FAS is a self-reported 10-item scale evaluating symptoms of chronic fatigue with lower scores indicating less fatigue. A negative change from the baseline indicates improvement. The FAS score also includes two subscales of physical fatigue and mental fatigue. There are five response options for each of the 10 items (never, sometimes, regularly, often or always). The secondary endpoint was the efficacy of vitamin D administration on fatigue using a short fatigue test called a fatigue course assessment (FCA). This is a five-item self-report where patients categorize their current level of fatigue as compared with its level at baseline: options include completely resolved, improved, unchanged, worse, or much worse. Those who met the enrollment criteria for fatigue completed a validated four-item basic questionnaire for fatigue (BQF), which was used to confirm fatigue symptoms at baseline; and they were eligible if two or more points were reached.

Patients were randomized to receive a single oral dose of 100,000 units of vitamin D or placebo. The follow-up visit was four weeks after the baseline visit and ingestion of the vitamin D. Over four weeks, the mean FAS decreased significantly more in the vitamin D group compared with the placebo (-3.3 vs -0.8) and was considered to improve significantly in the vitamin D group only. Resolution of fatigue was reported more frequently in the vitamin D group vs the placebo group (72% vs 50%). A greater improvement of FAS was associated with a greater increase in the 25(OH)D level. Improvement in fatigue at the four-week follow-up visit, as assessed by the self-reporting FCA, was 48% in the vitamin D-treated group vs 37% in the placebo group. A significant increase in 25(OH)D was observed in vitamin D-treated individuals but not in the placebo-treated participants.

Commentary: This appears to be the first double-blind randomized clinical trial that tested a one-time dose in individuals with fatigue due to no known physical or mental illness. While the mechanism by which vitamin D may improve fatigue is unknown, we do know that the vitamin D receptor is present in many parts of the brain. Central fatigue may arise from a dopamine imbalance within the central nervous system, and we know that vitamin D has dopaminergic effects. Vitamin D has also been shown to regulate brain serotonin synthesis and a defect in serotonergic function might also be associated with fatigue.

This 100,000 IU one-time dose led to a significant improvement in fatigue in the vitamin D-treated group, which correlated significantly with the change in serum levels of vitamin D. Patients with fatigue for no reason other than serum vitamin D level less than 20 mcg/L are a meaningful number of patients in a primary care practice. While this study is limited by its short-term follow-up, I will take this study into my clinical practice. I will also be interested to see if this approach would help those with vitamin D insufficiency (20-30 mcg/L serum 25(OH)D) rather than deficiency—an even larger group.

Nowak A, et al. Effect of vitamin D3 on self-perceived fatigue. A double-blind randomized placebo-controlled trial. *Medicine*. 2016;95.52.

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Women's Health Update

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Chondroitin Sulfate Similar to Celecoxib for Osteoarthritis of the Knee

Osteoarthritis (OA) is the most common musculoskeletal disease in humans, and OA of the knees and hips tends to be the most problematic and have the most impact on daily life, due to them being large weight-bearing joints. Conventional medical management includes analgesics and non-steroidal anti-inflammatory drugs (NSAIDS), both prescription and over-the-counter. However, these medications have cautionary and safety issues.

Chondroitin sulfate (CS) is available as a pharmaceutical grade and nutraceutical grade product. It is largely used by itself or in combination with glucosamine sulfate (GS) for the pain, inflammation, and loss of function caused by osteoarthritis. A Cochrane review in 2015 concludes that CS, alone or in combination with GS, is better than placebo in improving pain in those with OA in short-term studies.

There have been some discrepancies in the literature as to different qualities of CS and problematic trial designs. The current study, called the CONCEPT trial, investigates pharmaceutical grade CS in patients with symptomatic OA of the knee, and the trial is conducted according to guidelines on clinical investigations of medicinal products used in the treatment of osteoarthritis from the European Medicines Agency (EMA). The study included patients from several European countries who were over age 50 and had knee OA of the medial or lateral femorotibial compartment diagnosed by X-ray. The pain score of at least one knee had to be at least 50 mm on a 0-100 mm Visual Analogue Scale (VAS) for at least three months prior to study enrollment. There were numerous exclusion criteria that largely had to do with no recent treatments or injections of slow-acting drugs for OA, NSAIDS, or paracetamol.

Individuals were randomly assigned to one of three groups: 1) One tablet of CS 800 mg and one capsule of placebo; 2) One tablet of placebo CS and one capsule of celecoxib 200 mg (Celebrex); 3) placebo CS and placebo celecoxib one capsule of each. All treatments were taken daily for six months. Rescue pain meds were allowed with paracetamol (a maximum of 500 mg three times daily) and were recorded in a diary. No other pharmaceutical or non-pharmaceutical interventions for OA were allowed.

Of the 656 patients who were screened, 603 were eligible for analysis. Of these, 199 received CS, 199 received celecoxib, and 205 received placebo. The analysis of pain scored revealed a significant improvement in all three groups compared with baseline at days 30, 91, and 182; but both the CS and the celecoxib group showed similar and a statistically greater reduction in pain compared with placebo after six months. The Lequesne Index (LI), which integrates pain and function revealed a significant amelioration in all three groups; and at day 91 and 182, both CS and celecoxib caused a significantly greater reduction in LI than placebo with no difference between CS and celecoxib at day 91 and 182. Celecoxib was statistically different starting at day 30, compared to placebo, whereas the CS group took until day 91. After six months, a greater number of patients reached the minimally clinically important improvement of 20 m VAS reduction in the CS group (68%) and celecoxib group (69%) than in the placebo group (61%). CS and celecoxib offered similar results and had significantly higher number or responders than placebo.

Commentary: The authors point out that this is the first ever trial showing therapeutic benefit of a slow-acting intervention for OA of the knee in accordance with EMA guidelines. The results demonstrate that CS (800 mg/day) is superior to placebo and similar to celecoxib (200 mg/day) for reduction in pain and improvement in function. Therapeutic benefit at three months and beyond is where the interventions were statistically better than placebo.

When it comes to OA of the knees, CS should be considered as a primary natural medicine treatment. We can also include CS in the context of a comprehensive holistic approach of nutrition and exercise and with or without other natural medicine agents such as curcuminoids, boswellia, fish oils, glucosamine sulfate, and more.

Reginster J-Y, et al. Pharmaceutical-grade chondroitin sulfate is as effective as celecoxib and superior to placebo in symptomatic knee osteoarthritis: The ChONdroitin versus Celecoxib versus Placebo Trial (CONCEPT). *Annals of the Rheumatic Diseases*. 2017;76:1537-1543.

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Calendar

Please submit an announcement of your event 90 days in advance.
Event publication must be limited to 25 words or less. Multiple event listings require paid advertising.
Contact calendar@townsendletter.com for details.

DECEMBER 2: AUTISM – UNRAVELING THE MYSTERY with Dr. Court Vreeland in Charlotte, North Carolina. CONTACT: Biotics Research, 800-231-5777; http://www.BioticsResearch.com

DECEMBER 14-16: A4M & MMI WORLD CONGRESS in Las Vegas, Nevada. Pre-Conference on **DECEMBER 12-13**. CONTACT: 561-997-0112; https://www.a4m.com/world-congress-2017/home.html

JANUARY 12-14: MATRIX REFLEX TESTING (MRT) BASIC COURSE with Dr. Louisa Williams in Austin, Texas. CONTACT: info@radicalmedicine.com

JANUARY 25-FEBRUARY 9: INTENSIVE CLINICAL TRAINING IN INDIA in Calcutta, India. 200+ live cases demonstrated to show action of homeopathy in gross pathologies. CONTACT: http://www.homeopathy-course.com/index.php/training-courses/india-homoeopathy-training/2-week-clinical-training-in-calcutta

FEBRUARY 1-3: INSTITUTE FOR FUNCTIONAL MEDICINE – CARDIOMETABOLIC APM in Atlanta, Georgia. CONTACT: 800-228-0622; https://www.ifm.org/

FEBRUARY 4-6: INSTITUTE FOR FUNCTIONAL MEDICINE - IMMUNE APM in Atlanta, Georgia. CONTACT: 800-228-0622; https://www.ifm.org/

FEBRUARY 8-11: 15th ANNUAL NATURAL SUPPLEMENTS CONFERENCE in San Diego, California. CONTACT: https://www.scripps.org/event_schedules/1057-naturalsupplements

FEBRUARY 8-13: A4M & MMI present BIO-IDENTICAL HORMONE REPLACEMENT SYMPOSIUM in Charleston, South Carolina. CONTACT: https://www.a4m.com

FEBRUARY 9-11: LABRIX ADVANCED WORKSHOP in Las Vegas, Nevada. Adrenal/HPA axis hormone and neurotransmitter testing and treatment protocols. CONTACT: https://www.labrix.com/law

FEBRUARY 10-11: GREAT PLAINS LABORATORY PRACTITIONER WORKSHOPS – Organic Acids Testing and Environmental Toxin Testing in Austin, Texas. Also, **FEBRUARY 24-25** in Los Angeles, California, and **APRIL 13-15** in Chicago, Illinois. CMEs available. CONTACT: http://www.GPLUniversity.com

FEBRUARY 10-11: 2018 FOOD AS MEDICINE SYMPOSIUM @ National University of Natural Medicine in Portland, Oregon. CONTACT: http://career-alumni.nunm.edu/continuing-education/

MARCH 2-3: CLINICAL MITOCHONDRIAL AND ENVIRONMENTAL MEDICINE in Heidelberg, Germany. Specialist lectures in English. Also, first of 4 weekends for German curriculum. CONTACT: info@mito-medizin.de; http://www.mito-medizin.de/

MARCH 19-23: INSTITUTE FOR FUNCTIONAL MEDICINE - APPLYING FUNCTIONAL MEDICINE IN CLINICAL PRACTICE in San Diego, California. Also, **OCTOBER 1-5** in Washington, DC; **OCTOBER 4-8** in London, United Kingdom. CONTACT: 800-228-0622; https://www.ifm.org/

APRIL 5-7: THE FORUM FOR INTEGRATIVE MEDICINE – "Treating the Untreatable: Unraveling Complex Chronic Illness" in Chicago, Illinois. Register by Dec 31, 2017 for savings. CONTACT: forumforintegrativemedicine.org

APRIL 6-8: ENVIRONMENTAL HEALTH SYMPOSIUM 2018 in Scottsdale, Arizona. Effective methods and interventions for reducing toxic load and body burden. CONTACT: 855-347-4477; http://www.EHS2018.com

APRIL 6-8: 13th ANNUAL JOINT AMERICAN HOMEOPATHIC CONFERENCE – "Homeopathy: An Affordable Healthcare Solution" in Phoenix, Arizona. CONTACT: www.homeopathycenter.org

APRIL 12-14: A4M ANNUAL SPRING CONFERENCE in Hollywood, Florida. CONTACT: https://www.a4m.com/

APRIL 14-15: CALIFORNIA NATUROPATHIC DOCTORS ASSOCIATION with PsychANP present INTEGRATIVE PSYCHIATRY AND NEURO-IMMUNOLOGY in Torrance, California. CONTACT: www.calnd.org

APRIL 18-22: INTERNATIONAL COLLEGE OF INTEGRATIVE MEDICINE SPRING CONFERENCE – "What Works" in Cincinnati, Ohio. CONTACT: http://icimed.com/

APRIL 20-21: INTEGRATIVE MEDICINE FOR THE TREATMENT OF TICK-BORNE DISEASES in Baltimore, Maryland. CONTACT: delmarvalyme@yahoo.com; http://integrativelyme.com

APRIL 27-29: 47th ANNUAL INTERNATIONAL ORTHOMOLECULAR MEDICINE TODAY CONFERENCE in Tokyo, Japan. CONTACT: https://www.isom.ca/omt/

MAY 18-20: 5th ANNUAL TRADITIONAL ROOTS HERBAL CONFERENCE @ National University of Natural Medicine in Portland, Oregon. CONTACT: http://traditionalroots.org/tradrootscon2018/

MAY 31- JUNE 2: INSTITUTE FOR FUNCTIONAL MEDICINE ANNUAL INTERNATIONAL CONFERENCE in Hollywood, Florida. CONTACT: 800-228-0622; https://www.ifm.org/

JULY 6-8: 5th INTERNATIONAL CONGRESS ON NATUROPATHIC MEDICINE – Promoting Excellence in Natural Medicine in London, United Kingdom. CONTACT: + 44 (0)1745 828 400 Email: secretariat@icnmnaturopathy.eu; http://icnmnaturopathy.eu/en/

JULY 12-14: INSTITUTE FOR FUNCTIONAL MEDICINE – HORMONE APM in Portland, Oregon. CONTACT: 800-228-0622; https://www.ifm.org/

JULY 12-14: AMERICAN ASSOCIATION OF NATUROPATHIC PHYSICIANS ANNUAL CONVENTION AND EXPOSITION in San Diego, California. CONTACT: http://www.naturopathic.org/aanp2018

JULY 15-17: INSTITUTE FOR FUNCTIONAL MEDICINE – ENERGY APM in Portland, Oregon. CONTACT: 800-228-0622; https://www.ifm.org/

SEPTEMBER 14-15: CLINICAL MITOCHONDRIAL AND ENVIRONMENTAL MEDICINE in Heidelberg, Germany. Specialist lectures in English. CONTACT: info@mito-medizin.de; http://www.mito-medizin.de/

OCTOBER 18-22: INTERNATIONAL COLLEGE OF INTEGRATIVE MEDICINE – An Orthomolecular Approach to Cancer in Minneapolis, Minnesota. CONTACT: http://icimed.com/

OCTOBER 25-27: INSTITUTE FOR FUNCTIONAL MEDICINE – GASTROINTESTINAL APM in Nashville, Tennessee. CONTACT: 800-228-0622; https://www.ifm.org/

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Mercury and heavy metal toxicity is a widespread problem in the US. Mercury is commonly found throughout the environment and is easily taken up into the human body via inhalation and when ingested. The body has a hard time excreting mercury, and it slowly accumulates in organs, including the brain. Exposure to mercury can occur through air, soil, and water, fish/shellfish, vegetables, cosmetics and dental amalgams within our teeth. According to the *Journal of Occupational Medicine and Toxicology*, elemental mercury is found in approximately 50% of all dental fillings. Even more concerning is that unborn babies exposed to mercury in utero are the most severely affected, which is why it's very important for young women to be tested a substantial time before becoming pregnant so if mercury is found to be in excess it can be treated before the fetus is put at risk.

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Mushroom Wisdom Introduces New "Old" Mushroom – Super Poria

Mushroom Wisdom, Inc. (MWI) is pleased to announce its tenth addition to their 'Super' line of single mushroom extracts: Super Poria. With a very long history of use in traditional Chinese medicine, Poria is now being introduced to the West in a single full-spectrum concentrated extract. While new to many in the US, Poria is actually one of the most widely utilized ingredients in Chinese herbal formulas.

In traditional medicine Poria is primarily used to help remove "Damp" in the body. Dampness is a concept in traditional Chinese medicine not widely recognized in the West, which, as it turns out, is quite ironic since it is widespread in our culture. You can think of dampness as a "thick fog" that can build up in various parts and systems of our body, particularly the stomach, lungs, and kidneys, but also the brain – what we would call "brain fog."

As it is with virtually all mushrooms in current use in the West, Poria offers a range of encouraging immune supporting actions. However, more recently there has been new research into its promising use to support healthy kidney function.* Research has found Poria to offer several kidney supporting actions including the following:

- Antioxidant support for the kidneys,*
- Kidney function support,*
- Energetic support for kidneys,* and
- Contains a constituent called pachyman that research shows has specific kidney-supporting activity.*

MWI feels the time is right for an increasing focus on kidney health and function with its introduction of Super Poria.*

About Mushroom Wisdom, Inc.
Mushroom Wisdom celebrated its 25th anniversary this year as a leader in the mushroom category. MWI has been at the forefront of combining the wisdom of traditional medicine with the advances and knowledge of current scientific research. Best known for its innovative and unique extractions of research-based mushroom compounds, MWI also offers a diverse array of potent, single-mushroom, concentrated extracts.

* These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure or prevent any disease.

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Medical Education Needs to Improve

In the last issue of the *Townsend Letter,* I reviewed a study regarding the frequency with which obstetricians and nurse-midwives in the United States recommend iodine-containing multivitamins for pregnant and nursing women. Iodine deficiency is among the most common causes of impaired brain development in fetuses and infants. In the United States, the iodine status of pregnant women is considered on average to be mildly deficient. The Endocrine Society, the American Thyroid Association, the Teratology Society, and the American Academy of Pediatrics recommend that women receive prenatal vitamins providing 150 µg per day of iodine during preconception, pregnancy, and lactation. However, the study I reviewed found that, while most nurse-midwives and obstetricians recommended prenatal multivitamins, about two-thirds of them rarely or never recommended iodine-containing multivitamins for pregnant or nursing women.[1] Thus, most obstetricians and nurse-midwives are putting children at risk of subpar mental development by failing to advise their patients about a simple, safe, and low-cost intervention.

The only reason I can think of that presumably well-trained practitioners would neglect to provide this basic advice is that clinical training and continuing education programs do not emphasize the importance of iodine for fetal and child development and do not point out that the iodine nutrition status of many American women is marginal. A number of other examples come to mind of how inadequate training can lead to unsatisfactory outcomes. Many (though not all) of these examples are related to nutrition, which is not surprising, since nutrition education among medical professionals is embarrassingly poor. A few examples are described below.

Warfarin and Vitamin K

Warfarin is a frequently prescribed anticoagulant drug that works by inhibiting the vitamin K-dependent activation of coagulation factors II, VII, IX, and X. Because this inhibition is competitive in nature, the effect of warfarin is influenced by dietary vitamin K intake. Increasing vitamin K intake inhibits the action of warfarin, whereas decreasing vitamin K intake has the opposite effect. For this reason, experts recommend that patients taking warfarin keep their dietary intake of vitamin K consistent. Moreover, studies have shown that supplementing with 100-150 µg per day of vitamin K_1 results in fewer fluctuations of the International Normalized Ratio (INR) outside the normal range, thereby reducing the risk of thrombotic events resulting from under-treatment and the risk of hemorrhagic events resulting from over-treatment. Vitamin K supplementation probably improves the stability of anticoagulation by decreasing the relative change in total vitamin K intake associated with variations in dietary vitamin K.[2,3]

Despite this evidence and despite the recommendations made by experts, many practitioners advise patients taking warfarin to restrict dietary vitamin K intake. In a recent study, of 317 patients enrolled in the Quebec Warfarin Cohort Study in 2011-2012, 68% reported being advised to limit or avoid vitamin K-rich foods, particularly green vegetables.[4] That advice is inappropriate for two reasons. First, as noted above, vitamin K supplementation results in fewer fluctuations of INR

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values. Second, restricting vitamin K intake requires the avoidance of leafy green vegetables, which decreases the quality of the diet. Most patients taking warfarin have cardiovascular disease, and leafy green vegetables provide many cardioprotective micronutrients.

Vitamin A and Bronchopulmonary Dysplasia

Premature infants are at risk of developing bronchopulmonary dysplasia, a chronic and potentially serious lung disease. In a large randomized trial, intramuscular administration of vitamin A to extremely-low-birth-weight premature infants significantly decreased the incidence of bronchopulmonary dysplasia by 11%.[5] However, a survey conducted in the United States revealed that only about one in six neonatologists recommend routine vitamin A prophylaxis. The investigators who conducted that survey pointed out that their findings indicate that neonatologists are inconsistent in their use of evidence-based medicine, since they often administer other treatments on the basis of weaker evidence of safety and benefit than that which supports vitamin A supplementation.[6]

The Cisapride Fiasco

Cisapride is a drug used to increase gastrointestinal motility. It was approved by the FDA in 1993 for the treatment of nocturnal heartburn. By 1995, approximately 5 million prescriptions per year were being filled for this drug. However, by that time more than 50 cases of cardiac arrhythmias and four deaths had been reported in users of the drug. The FDA ruled that cisapride was contraindicated in certain circumstances: 1) in patients taking medications that interfere with cisapride metabolism (e.g., drugs that inhibit the cytochrome P450-3A4 enzymes), 2) in patients taking medications that prolong the QT interval on the electrocardiogram, and 3) in patients with diseases that predispose to certain cardiac arrhythmias. A black-box warning to this effect was placed in the *Physicians' Desk Reference*, and the manufacturer sent a letter to all doctors.

Despite these warnings, there was only a minor reduction in contraindicated use of this drug. In a study published in 2000, the appropriateness of cisapride use was assessed at two managed-care organizations and one state Medicaid program, both before and after the FDA instituted its educational campaign.[7] The evaluation included more than 22,000 cisapride prescriptions during each period. In the year prior to the FDA's effort at educating doctors, cisapride use was contraindicated for 25%, 30%, and 60% of users at the three sites, respectively, with the worst results being seen in the Medicaid patients. In the year after the FDA attempted to educate the medical community, these numbers changed only slightly: to 24%, 28%, and 58%, respectively. Because doctors were continuing to risk patients' lives by prescribing cisapride inappropriately, the manufacturer was forced to remove the drug from the market.

What We Can Do

There are no easy ways to overcome this type of incompetence in the delivery of healthcare. It would probably be helpful to create a task force charged with identifying common mistakes made by healthcare professionals. This information could be incorporated into the medical school curriculum and could be made a required component of continuing education for licensed practitioners. Irrespective of any improvements in the medical education system, it is incumbent upon healthcare practitioners to become more knowledgeable about nutrition and to have a working knowledge of the side effects, interactions, and contraindications of all drugs they prescribe.

Alan R. Gaby, MD

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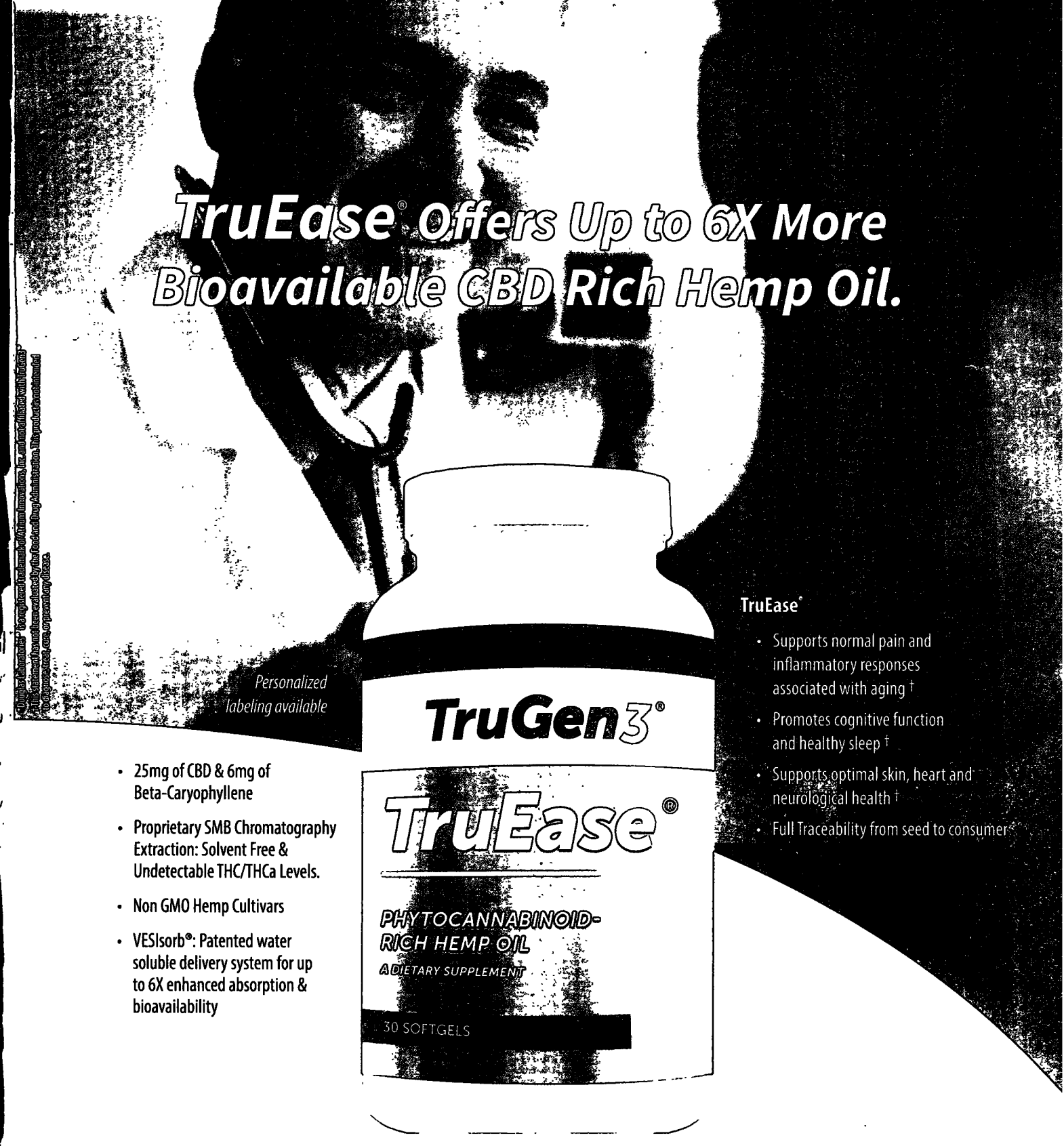

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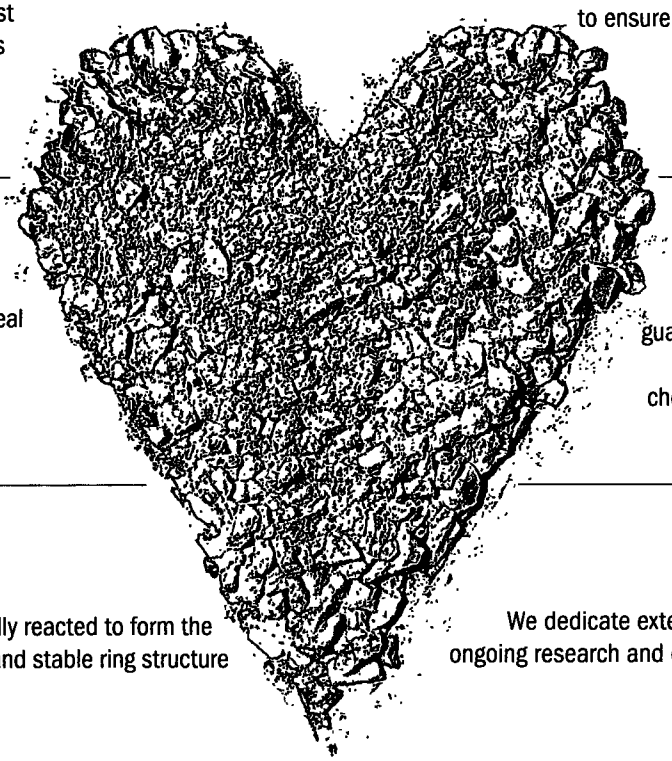

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